HELENE C. CARLSON
ATTORNEY
(202) 772-8641
HCARLSON@SKGF.COM

DAC 4

Sterne Kessler Goldstein Fox
ATTORNEYS AT LAW

November 10, 2010

Commissioner for Patents
U.S. Patent and Trademark Office
Mail Stop Patent Extension
Randolph Building
401 Dulany Street
Alexandria, VA 22314

Re: U.S. Patent Application No. 6,783,965; Issue Date: August 31, 2004
For: **Aggregate-free urate oxidase for preparation of non-immunogenic polymer conjugates**
Inventors: Sherman *et al.*
Our Ref: 2057.0080000/ELE/HCC

Sir:

Transmitted herewith for appropriate action are the following documents:

1. Credit Card Payment Form (PTO-2038) in the amount of $1,120.00 to cover fee for Application for Extension of Patent Term Pursuant to 35 U.S.C. §156;

2. Application for Extension of Patent Term Pursuant to 35 U.S.C. §156, signed by Mark G.P. Saifer, Ph.D., of Mountain View Pharmaceuticals, Inc. *(in triplicate)*, and Exhibits 1-13 *(each in triplicate)*;

3. Application for Extension of Patent Term Pursuant to 35 U.S.C. §156, signed by Robert L. Taber, Ph.D., of Duke University *(in triplicate)*, and Exhibits 1-13 *(each in triplicate)*; and

4. One (1) return postcard.

It is respectfully requested that the attached postcard be stamped with the date of filing of these documents, and that it be returned to our courier.

In the event that extensions of time are necessary to prevent abandonment of this patent application, then such extensions of time are hereby petitioned.

The U.S. Patent and Trademark Office is hereby authorized to charge any fee deficiency, or credit any overpayment, to our Deposit Account No. 19-0036.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

Helene C. Carlson
Attorney for Applicants
Registration No. 47,473

ELE/HCC/las
Enclosures

1282151_1.DOC

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re United States Patent No. 6,783,965
Granted: August 31, 2004

Patentees: Merry R. Sherman, Mark G. P. Saifer, L. David Williams, Michael S. Hershfield, Susan J. Kelly

Assignees: Mountain View Pharmaceuticals, Inc.
Duke University

For: Aggregate-free urate oxidase for preparation of non-immunogenic polymer conjugates

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APPLICATION FOR EXTENSION OF PATENT TERM
PURSUANT TO 35 U.S.C. § 156

Sir:

Pursuant to Section 201(a) of the Drug Price Competition and Patent Term Restoration Act of 1984, 35 U.S.C. § 156(a), Mountain View Pharmaceuticals, Inc. and Duke University (collectively, "Applicants") hereby request an extension of the patent term of United States Patent No. 6,783,965 ("the '965 Patent").

Applicants represent that they are the record owners of the entire interest in the '965 Patent, by virtue of assignments from the inventors thereof recorded in the United States Patent and Trademark Office (Reel/Frames: 10836/0572-0574 and 17663/0313-0315) with respect to the patent application leading thereto as documented in **Exhibit 1** hereto.

Inquiries and correspondence relating to this application are to be directed as set forth in section (15) below.

The holder of marketing approval for KRYSTEXXA™ (pegloticase), the Approved Product that is relevant to this application, is Savient Pharmaceuticals, Inc. of East Brunswick, New Jersey, the exclusive licensee of the '965 Patent. Applicants are authorized to rely upon the activities of Savient Pharmaceuticals, Inc. before the U.S. Food and Drug Administration ("FDA") for this application for extension of patent term of the '965 Patent as documented in **Exhibit 2** hereto.

The following information is submitted in accordance with 35 U.S.C. § 156(d) and 37 C.F.R. § 1.710 et seq., and for the convenience of the United States Patent and Trademark Office, the information in this application is presented in the order and format as set forth in 37 C.F.R. § 1.740(a):

(1) A complete identification of the approved product as by appropriate chemical and generic name, physical structure or characteristics;

The Approved Product, KRYSTEXXA™ (pegloticase), is a PEGylated uric acid specific enzyme for administration by intravenous infusion for the treatment of chronic gout in adult patients refractory to conventional therapy. Gout refractory to conventional therapy occurs in patients who have failed to normalize serum uric acid and whose signs and symptoms are inadequately controlled with xanthine oxidase inhibitors at the maximum medically appropriate dose or for whom these drugs are contraindicated.

The chemical names of KRYSTEXXA include: Oxidase, urate (synthetic *Sus scrofa* variant pigKS-ΔN subunit), homotetramer, amide with α-carboxy-ω-methoxypoly(oxy-1,2-ethanediyl); and des-(1-6)-[7-threonine,46-threonine,291-lysine,301-serine]uricase (EC 1.7.3.3, urate oxidase) *Sus scrofa* (pig) tetramer, non acetylated, carbamates with α-carboxy-ω-methoxypoly(oxyethylene). The peptide monomer sequence of KRYSTEXXA is:

```
TYKKNDEVEFVRTGYGKDMIKVLHIQRDGKYHSIKEVATTVQLTLSSKKD    50

YLHGDNSDVIPTDTIKNTVNVLAKFKGIKSIETFAVTICEHFLSSFKHVI    100

RAQVYVEEVPWKRFEKNGVKHVHAFIYTPTGTHFCEVEQIRNGPPVIHSG    150

IKDLKVLKTTQSGFEGFIKDQFTTLPEVKDRCFATQVYCKWRYHQGRDVD    200

FEATWDTVRSIVLQKFAGPYDKGEYSPSVQKTLYDIQVLTLGQVPEIEDM    250

EISLPNIHYLNIDMSKMGLINKEEVLLPLDNPYGKITGTVKRKLSSRL      300
```

Approximately 10 out of the 30 lysine residues of the peptide monomer are PEGylated.

See Approved Label attached as **Exhibit 3** with regard to the statements in this Section (1).

(2) A complete identification of the Federal statute including the applicable provision of law under which the regulatory review occurred;

The Approved Product is a drug product and the submission was approved under Section 351 of the United States Public Health Service Act (42 U.S.C. § 262).

(3) An identification of the date on which the product received permission for commercial marketing or use under the provision of law under which the applicable regulatory review period occurred;

The Approved Product KRYSTEXXA™ received permission for commercial marketing or use under Section 351 of the Public Health Service Act (42 U.S.C. § 262) upon approval of Biologics License Application ("BLA"), STN: BLA 125293, on September 14, 2010.

A copy of the FDA approval letter is attached as **Exhibit 4**.

(4) **In the case of a drug product, an identification of each active ingredient in the product and as to each active ingredient, a statement that it has not been previously approved for commercial marketing or use under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act, or a statement of when the active ingredient was approved for commercial marketing or use (either alone or in combination with other active ingredients), the use for which it was approved, and the provision of law under which it was approved.**

As active ingredient, a single dose of the Approved Product KRYSTEXXA™ contains a clear, colorless, sterile 8 mg/mL solution of pegloticase in a 2 mL single-use vial, expressed as amounts of uricase protein.

Neither the Approved Product KRYSTEXXA™ nor the active ingredient pegloticase has been previously approved for commercial marketing or use under the Food, Drug, and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act.

(5) **A statement that the application is being submitted within the sixty day period permitted for submission pursuant to §1.720(f) and an identification of the date of the last day on which the application could be submitted;**

KRYSTEXXA™ was approved on September 14, 2010, and the last day within the sixty day period permitted for submission of an application for patent term extension is November 12, 2010, which is subsequent to the date on which this application has been submitted.

(6) **A complete identification of the patent for which an extension is being sought by the name of the inventor, the patent number, the date of issue, and the date of expiration;**

Name of the inventors:	Merry R. Sherman, Mark G. P. Saifer, L. David Williams, Michael S. Hershfield, Susan J. Kelly
Patent number:	6,783,965
Date of issue:	August 31, 2004
Date of expiration:	August 6, 2019

(7) **A copy of the patent for which an extension is being sought, including the entire specification (including claims) and drawings;**

A full copy of U.S. Patent No. 6,783,965, for which extension is being sought, is attached as **Exhibit 5**.

(8) **A copy of any disclaimer, certificate of correction, receipt of maintenance fee payment, or reexamination certificate issued in the patent;**

A copy of a Terminal Disclaimer dated December 4, 2003 is attached as **Exhibit 6**. A copy of a Terminal Disclaimer dated August 5, 2008 is attached as **Exhibit 7**. A copy of a Certificate of Correction dated December 19, 2006 is attached as **Exhibit 8**. A copy of a Certificate of Correction dated September 1, 2009 is attached as **Exhibit 9**. A statement showing maintenance fee payment for pay year 04 is attached as **Exhibit 10**. Maintenance fee payments for pay years 08 and 12 are not yet due.

(9) **A statement that the patent claims the approved product, or a method of using or manufacturing the approved product, and a showing which lists each applicable patent claim and demonstrates the manner in which at least one such patent claim reads on the approved product, or a method of using or manufacturing the approved product:**

Claims 1, 4, 6, 7, 16, 17, 18, 19, 20, 21, 22, 24, 26, 28, 29 and 30 of the '965 Patent read on the approved product as detailed below.

Claim	Demonstration
1. Purified urate oxidase (uricase) that contains no more than about 2% of aggregates larger than octamers, wherein greater than about 20% of said uricase is in the tetrameric or octameric form.	KRYSTEXXA™ contains purified urate oxidase (uricase) that has no more than about 2% of aggregates larger than octamers, wherein greater than about 20% of said uricase is in the tetrameric or octameric form.
4. The uricase of claim 1, wherein the uricase is recombinant.	KRYSTEXXA™ contains recombinant uricase.
6. The uricase of claim 4, wherein the uricase is chimeric.	KRYSTEXXA™ contains chimeric uricase.
7. The uricase of claim 6, wherein the chimeric uricase contains portions of porcine liver and baboon liver uricase.	KRYSTEXXA™ contains chimeric uricase containing portions of porcine liver and baboon liver uricase.
16. A uricase conjugate comprising the uricase of claim 1 conjugated to poly(ethylene glycol) or poly(ethylene oxide).	KRYSTEXXA™ contains purified urate oxidase (uricase) conjugated to poly(ethylene glycol).
17. The uricase conjugate of claim 16, wherein said poly(ethylene glycol) is monomethoxy poly(ethylene glycol).	KRYSTEXXA™ contains purified urate oxidase (uricase) conjugated to monomethoxy poly(ethylene glycol).
18. The uricase conjugate of claim 16, wherein said uricase is conjugated to said poly(ethylene glycol) or poly(ethylene oxide) via a linkage selected from the group consisting of urethane (carbamate), secondary amine and amide.	KRYSTEXXA™ contains purified urate oxidase (uricase) conjugated to poly(ethylene glycol) via a urethane (carbamate) linkage.
19. The uricase conjugate of claim 16, wherein said poly(ethylene glycol) or poly(ethylene oxide) has a molecular weight between about 5 kDa and 30 kDa.	KRYSTEXXA™ contains purified urate oxidase (uricase) conjugated to poly(ethylene glycol) of molecular weight between about 5 kDa and 30 kDa.
20. The uricase conjugate of claim 19, wherein said poly(ethylene glycol) or poly(ethylene oxide) has a molecular weight between about 10 kDa and 20 kDa.	KRYSTEXXA™ contains purified urate oxidase (uricase) conjugated to poly(ethylene glycol) of molecular weight between about 10 kDa and 20 kDa.
21. The uricase conjugate of claim 16, wherein the average number of strands of said poly(ethylene glycol) or poly(ethylene oxide) is between about 2 and 12 per uricase subunit.	KRYSTEXXA™ contains purified urate oxidase (uricase) conjugated to between an average of about 2 and 12 strands of poly(ethylene glycol) per uricase subunit.

22. The uricase conjugate of claim 21, wherein the average number of strands of said poly(ethylene glycol) or poly(ethylene oxide) is between about 6 and 10 per uricase subunit.	KRYSTEXXA™ contains purified urate oxidase (uricase) conjugated to between an average of about 6 and 10 strands of poly(ethylene glycol) per uricase subunit.
24. The uricase conjugate of claim 16, wherein the poly(ethylene glycol) or poly(ethylene oxide) is linear.	KRYSTEXXA™ contains purified urate oxidase (uricase) conjugated to linear poly(ethylene glycol).
26. A pharmaceutical composition for lowering uric acid levels in a body fluid or tissue, comprising the conjugate of claim 16 and a pharmaceutically acceptable carrier.	KRYSTEXXA™ is a pharmaceutical solution containing purified urate oxidase (uricase) conjugated to poly(ethylene glycol). KRYSTEXXA™ is approved for administration by intravenous infusion for the treatment of chronic gout in adult patients refractory to conventional therapy. See Approved Label attached as **Exhibit 3**. KRYSTEXXA™ treats chronic gout by lowering uric acid levels in a body fluid or tissue.
28. A purified fragment of uricase that contains no more than about 2% of aggregates larger than octamers, wherein said fragment is a recombinant uricase that has been truncated at the amino terminus, at the carboxyl terminus, or at both the amino and carboxyl termini, and wherein greater than about 20% of said truncated uricase is in the tetrameric or octameric form.	KRYSTEXXA™ contains purified, recombinant urate oxidase (uricase) that has been truncated at the amino terminus. Greater than about 20% of the purified uricase in KRYSTEXXA™ is in the tetrameric or octameric form and it has no more than about 2% of aggregates larger than octamers.
29. The purified uricase of claim 1, wherein about 98% to about 100% of said uricase is in the tetrameric or octameric form.	KRYSTEXXA™ contains purified urate oxidase (uricase) that is about 98% to about 100% in the tetrameric or octameric form.
30. Isolated uricase prepared by a method comprising separating uricase aggregates larger than octamers from uricase tetramers and octamers and excluding such aggregates from the isolated uricase, wherein about 98% to about 100% of said uricase is in the tetrameric or octameric form.	KRYSTEXXA™ contains isolated uricase prepared by a method comprising separating uricase aggregates larger than octamers from uricase tetramers and octamers and excluding such aggregates from the isolated uricase. KRYSTEXXA™ contains isolated uricase that is about 98% to about 100% in the tetrameric or octameric form.

(10) A statement beginning on a new page of the relevant dates and information pursuant to 35 U.S.C. 156(g) in order to enable the Secretary of Health and Human Services or the Secretary of Agriculture, as appropriate, to determine the applicable regulatory review period as follows:

(i) For a patent claiming a human drug, antibiotic, or human biological product:

(A) The effective date of the investigational new drug (IND) application and the IND number;

The first IND application for the approved product was submitted to the FDA by Bio-Technology General Corporation (the predecessor of Savient Pharmaceuticals, Inc., which is the exclusive licensee of the '965 Patent) on November 15, 2001. By letter dated November 30, 2001, the FDA acknowledged receipt of the IND application on November 19, 2001, and assigned IND number BB-IND 10122, resulting in an IND effective date of December 19, 2001. A copy of the FDA acknowledgement letter is attached as **Exhibit 11**.

Under these circumstances, the "regulatory review period" under 35 U.S.C. § 156(g)(1) began on **December 19, 2001**, the effective date of BB-IND 10122.

(B) The date on which a new drug application (NDA) or a Product License Application (PLA) was initially submitted and the NDA or PLA number; and

The BLA for KRYSTEXXA™ was initially submitted by Savient Pharmaceuticals, Inc. to the FDA on October 31, 2008. By letter dated November 12, 2008, the FDA acknowledged receipt of the BLA on October 31, 2008, and assigned Submission Tracking Number (STN): BLA 125293, as confirmed by **Exhibit 12**. This establishes **October 31, 2008** as the initial submission date of the BLA for the approved product for purposes of 35 U.S.C. § 156(g)(1).

(C) The date on which the NDA was approved or the Product License issued;

The BLA for KRYSTEXXA™ was approved by the FDA approval letter dated and sent September 14, 2010, setting the effective date of the approval as the September 14, 2010 date of the letter. A copy of this FDA approval letter is attached as **Exhibit 4**. This establishes the end of the "regulatory review period" under 35 U.S.C. 156(g)(1) as **September 14, 2010**.

(11) **A brief description beginning on a new page of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities;**

A listing of the significant activities undertaken by the marketing applicant, and their respective dates, with respect to the approved product during the applicable regulatory review period of BB-IND 10122 and BLA 125293 is attached as **Exhibit 13**, the disclosure of which is incorporated herein in its entirety.

(12) **A statement beginning on a new page that in the opinion of the applicant the patent is eligible for the extension and a statement as to the length of extension claimed, including how the length of extension was determined;**

Statement That the Patent Is Eligible For Extension

Applicants are of the opinion that U.S. Patent No. 6,783,965 is eligible for extension under 35 U.S.C. § 156(a) because it satisfies all of the requirements for such extension as follows:

(1) 35 U.S.C. 156(a)

U.S. Patent No. 6,783,965 claims the approved product as detailed in Section (9) above.

(2) 35 U.S.C. 156 (a)(l)

U.S. Patent No. 6,783,965 was granted on August 31, 2004 on an earliest filed U.S. application filed on February 10, 2000. A terminal disclaimer was filed with regard to U.S. Patent No. 6,576,235, which application was filed on August 6, 1999, with no terminal disclaimers. As such, the patent expires on August 6, 2019, being 20 years from filing of U.S. Patent No. 6,576,235. This application, therefore, has been submitted before the expiration of the patent term of the '965 Patent.

(3) 35 U.S.C. 156(a)(2)

The term of the '965 Patent has never been extended.

(4) 35 U.S.C. 156(a)(3)

This application is being submitted by the owners of record of U.S. Patent No. 6,783,965 through an assignment from the inventors as detailed on pages 1-2 above and in **Exhibit 1**, in accordance with the requirement of 35 U.S.C. 156(d) and rules of the U.S. Patent and Trademark Office.

(5) 35 U.S.C. 156(a)(4)

As evidenced by the September 14, 2010 approval letter from the FDA (**Exhibit 4**), KRYSTEXXA™ was subject to a regulatory review period under Section 351 of the Public Health Service Act (42 U.S.C. § 262) before its commercial marketing or use.

(6) 35 U.S.C. 156(a)(5)(A)

The permission for commercial marketing of KRYSTEXXA™ after this regulatory review period is the first permitted commercial marketing of the approved product or any active ingredient thereof, under provision of the Public Health Service Act (42 U.S.C. § 262) under which the regulatory review period occurred, as confirmed by the absence of any approved BLA for the approved product or any active ingredient thereof prior to September 14, 2010.

(7) 35 U.S.C. 156(a)(5)(B)

No other patent has been extended for the same regulatory review period for the product KRYSTEXXA™.

Statement Regarding Length of Extension Claimed

The term of U.S. Patent 6,783,965 should be extended **1445 days** from August 6, 2019 to **July 21, 2023**. In accordance with the implementing regulations of 37 C.F.R. 1.775 with respect to patent term extensions for a human drug product, the term extension of U.S. Patent No. 6,783,965 based on the regulatory review of KRYSTEXXA™ was determined as follows:

> **Section 1.775 Calculation of patent term extension for a human drug, antibiotic drug or human biological product.**
>
> **(a) If a determination is made pursuant to §1.750 that a patent for a human drug, antibiotic drug or human biological product is eligible for extension, the term shall be extended by the time as calculated in days in the manner indicated by this section. The patent term extension will run from**

the original expiration date of the patent or any earlier date set by terminal disclaimer (§1.321).

U.S. Patent No. 6,783,965 issued on August 31, 2004 from an earlier filed U.S. application filed on February 10, 2000. A terminal disclaimer was filed with regard to U.S. Patent No. 6,576,235, application for which was filed on August 6, 1999, with no terminal disclaimers. Pursuant to 35 U.S.C. 154(a)(2), this patent is entitled to an original term of 20 years from filing of the application for U.S. Patent No. 6,576,235 on August 6, 1999, which provides an original expiration date of August 6, 2019.

(b) The term of the patent for a human drug, antibiotic drug or human biological product will be extended by the length of the regulatory review period for the product as determined by the Secretary of Health and Human Services, reduced as appropriate pursuant to paragraphs (d)(1) through (d)(6) of this section.

(c) The length of the regulatory review period for a human drug, antibiotic drug or human biological product will be determined by the Secretary of Health and Human Services. Under 35 U.S.C. 156(g)(1)(B), it is the sum of —

(1) The number of days in the period beginning on the date an exemption under subsection (i) of section 505 or subsection (d) of section 507 of the Federal Food, Drug, and Cosmetic Act became effective for the approved product and ending on the date the application was initially submitted for such product under those sections or under section 351 of the Public Health Service Act; and

(2) The number of days in the period beginning on the date the application was initially submitted for the approved product under section 351 of the Public Health Service Act, subsection (b) of section 505 or section 507 of the Federal Food, Drug, and Cosmetic Act and ending on the date such application was approved under such section.

The number of days in the IND testing period of paragraph (c)(1) extends from the effective date of BB-IND 10122 on December 19, 2001 to the filing (receipt) of STN:BLA 125293 on October 31, 2008, being **2509 days**.

The number of days in the NDA approval period of paragraph (c)(2) extends from the filing of STN:BLA 125293 on October 31, 2008 to the date of approval of STN:BLA 125293 on September 14, 2010, being **684 days**.

The regulatory review period is the sum of the periods of paragraphs (c)(1) and (c)(2), being **3193 days**.

> **(d) The term of the patent as extended for a human drug, antibiotic drug or human biological product will be determined by —**
>
> **(1) Subtracting from the number of days determined by the Secretary of Health and Human Services to be in the regulatory review period:**
>
> **(i) The number of days in the periods of paragraphs (c)(1) and (c)(2) of this section which were on and before the date on which the patent issued;**
>
> **(ii) The number of days in the periods of paragraphs (c)(1) and (c)(2) of this section during which it is determined under 35 U.S.C. 156(d)(2)(B) by the Secretary of Health and Human Services that applicant did not act with due diligence;**
>
> **(iii) One-half the number of days remaining in the period defined by paragraph (c)(1) of this section after that period is reduced in accordance with paragraphs (d)(1) (i) and (ii) of this section; half days will be ignored for purposes of subtraction;**

With respect to paragraph (d)(1)(i), the number of days in the periods of paragraphs (c)(1) and (c)(2) on and before August 31, 2004 on which U.S. Patent No. 6,783,965 issued is from the effective date of BB-IND 10122 on December 19, 2001 to the issue of U.S. Patent No. 6,783,965 on August 31, 2004, being **987 days**.

With respect to paragraph (d)(1)(ii), 35 U.S.C. 156 (d)(2)(B) provides that if a petition is submitted to the Secretary not later than 180 days after publication of the determination of the applicable regulatory review period, upon which it may reasonably be determined that the applicant did not act with due diligence during the applicable regulatory review period, the Secretary shall determine if the applicant acted with due diligence during the

applicable regulatory review period. The Secretary making this determination shall notify the Director of the determination and shall publish in the Federal register a notice of such determination together with the factual and legal basis for such determination. Any interested person may request, within the 60-day period beginning on the publication of a determination, the Secretary to hold an informal hearing on the determination. If such request is made within such period, the Secretary shall hold such hearing, and shall provide notice of the hearing to the owner of the patent involved and to any interested person and provide the owner and any interested person an opportunity to participate in the hearing. Within 30 days after the completion of the hearing, the secretary shall affirm or revise the determination which was the subject of the hearing and shall notify the Director of any revision of the determination and shall publish any such revision in the Federal Register. There has been no such petition or determination by the Secretary, and thus the number of days under (d)(1)(ii) is **0 (zero) days**.

With respect to paragraph (d)(1)(iii), one-half the number of days remaining in the period defined by paragraph (c)(1) – **2509 days** – after that period is reduced in accordance with paragraphs (d)(1) (i) – **987 days** – and (d)(1) (ii) – **0 days** – is **761 days**, ignoring the half day.

Subtracting from the regulatory review period of **3193 days** as determined above pursuant to section 1.775(c) the number of days determined above with respect to sections 1.775(d)(1)(i), (ii) and (iii), the term of patent extension *for U.S. Patent No. 6,783,965* is **3193 days** minus **987 days** minus **0 (zero) days** minus **761 days** for a sum total of **1445 days**.

(2) By adding the number of days determined in paragraph (d)(1) of this section to the original term of the patent as shortened by any terminal disclaimer;

The original expiration date of U.S. Patent No. 6,783,965 is August 6, 2019 after being shortened by terminal disclaimer. Adding the **1445 days** determined in sections 1.775(d)(1) to the original term of the patent results in an extended term to **July 21, 2023**.

(3) By adding 14 years to the date of approval of the application under section 351 of the Public Health Service Act, or subsection (b) of section 505 or section 507 of the Federal Food, Drug, and Cosmetic Act;

Adding 14 years to the September 14, 2010 date of approval of the BLA results in the date September 14, 2024.

(4) By comparing the dates for the ends of the periods obtained pursuant to paragraphs (d)(2) and (d)(3) of this section with each other and selecting the earlier date;

The earlier date of **July 21, 2023** and September 14, 2024 is **July 21, 2023**.

(5) If the original patent was issued after September 24, 1984,

(i) By adding 5 years to the original expiration date of the patent or any earlier date set by terminal disclaimer; and

(ii) By comparing the dates obtained pursuant to paragraphs (d)(4) and (d)(5)(i) of this section with each other and selecting the earlier date;

Adding 5 years to the original expiration date of the patent of August 6, 2019 gives a date of August 6, 2024. The earlier date of **July 21, 2023** and August 6, 2024 is **July 21, 2023**.

Thus, as calculated above, the term of U.S. Patent No. 6,783,965 is eligible for a **1445 days** extension to **July 21, 2023**.

(13) A statement that applicant acknowledges a duty to disclose to the Director of the United States Patent and Trademark Office and the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to the determination of entitlement to the extension sought (see §1.765);

Applicants acknowledge a duty to disclose to the Director of the United States Patent and Trademark Office and the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to the determination of entitlement to the extension sought.

(14) The prescribed fee for receiving and acting upon the application for extension (see §1.20(j)); and

The Patent and Trademark Office is authorized to charge the filing fee of $1,120.00 and any additional fees which may be required by this or any other related paper, or to credit any overpayment to Deposit Account No. 19-0036.

(15) The name, address, and telephone number of the person to whom inquiries and correspondence relating to the application for patent term extension are to be directed.

Eldora Ellison Floyd, Reg. No. 39,967
Helene C. Carlson, Reg. No. 47,473
Sterne, Kessler, Goldstein & Fox, PLLC
1100 New York Avenue, NW
Washington, DC 20005
(202) 371-2600

FOR: Mountain View Pharmaceuticals, Inc.

SIGNATURE: Mark Saifer

BY: Mark G.P. Saifer, Ph.D.

TITLE: Vice President and Scientific Director

DATE: November 5, 2010

FOR: Duke University

SIGNATURE: _____

BY: H. Gilbert Smith, Ph.D.

TITLE: Managing Director

DATE: _____

EXHIBIT 1

Client Code: MVIEW.005A

MHD 5.22.00

RE 06-12-2000 :T

101378676

TO THE ASSISTANT COMMISSIONER FOR ocuments or copy thereof.

1. Name of conveying party(ies): (If multiple a... numerically)

Merry R. Sherman, Ph.D., Mark G.P. Saifer, Ph.D., and L. David Williams, Ph.D.

Additional name(s) of conveying party(ies) attached?
( ) Yes (X) No

... of receiving party(ies):

Name: Mountain View Pharmaceuticals, Inc.
Internal Address:
Street Address: 3475 S-Edison Way
City: Menlo Park **State:** CA **ZIP:** 94025

Additional name(s) of receiving party(ies) attached?
( ) Yes (X) No

3. Nature of conveyance:

(X) Assignment
( ) Merger
( ) Security Agreement
( ) Change of Name
( ) Other:

Execution Date: (If multiple assignors, list execution dates in numerical order corresponding to numbers indicated in 1 above) 1) April 26, 2000, 2) April 26, 2000 and 3) April 26, 2000

4. Application number(s) or Patent number(s):

( ) Application(s) filed herewith Execution Date(s):

(X) Patent Application No.: 09/501,730
Filing Date: February 10, 2000

( ) Patent No.:
Issue Date:

Additional numbers attached? ( ) Yes (X) No

5. Name and address of party to whom correspondence concerning document should be mailed:

Name: Dale C. Hunt
KNOBBE, MARTENS, OLSON & BEAR, LLP
Customer No. 20,995
Internal Address: Sixteenth Floor
Street Address: 620 Newport Center Drive
City: Newport Beach **State:** CA **ZIP:** 92660
Attorney's Docket No.: MVIEW.005A

7. Total fee (37 CFR 3.41): $40

(X) Enclosed
(X) Authorized to be charged to deposit account if any additional fees are required, or to credit any overpayment

8. Deposit account number: 11-1410

Please charge this account for any additional fees which may be required, or credit any overpayment to this account.

6. Total number of applications and patents involved: 1

9. Statement and signature.

To the best of my knowledge and belief, the foregoing information is true and correct, and any attached copy is a true copy of the original document.

Dale C. Hunt
Name of Person Signing

Signature

19 May 2000
Date

41,857
Registration No.

Total number of pages including cover sheet, attachments and document: 3

Mail documents to be recorded with required cover sheet information to:

06/12/2000 ASCOTT 00000060 09501730
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Assistant Commissioner for Patents
Box Assignments
Washington, D.C. 20231

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ASSIGNMENT

WHEREAS, We, Merry R. Sherman, Ph.D., a United States citizen, residing at 1114 Royal Lane, San Carlos, CA 94070; Mark G.P. Saifer, Ph.D., a United States citizen, residing at 1114 Royal Lane, San Carlos, CA 94070; and L. David Williams, Ph.D., a United States citizen, residing at 37709 Arlene Court, Fremont, CA 94536, have invented certain new and useful improvements in a AGGREGATE-FREE URATE OXIDASE FOR PREPARATION OF NON-IMMUNOGENIC POLYMER CONJUGATES for which we have filed an application for Letters Patent in the United States, 09/501,730, February 10, 2000;

AND WHEREAS, Mountain View Pharmaceuticals, Inc. (hereinafter "ASSIGNEE"), a California Corporation, with its principal place of business at 3475-S Edison Way, Menlo Park, California 94025, desires to acquire the entire right, title, and interest in and to the said improvements and the said Application:

NOW, THEREFORE, in consideration of the sum of One Dollar ($1.00) to me in hand paid, and other good and valuable consideration, the receipt of which is hereby acknowledged, we, the said inventors, do hereby acknowledge that we have sold, assigned, transferred and set over, and by these presents do hereby sell, assign, transfer and set over, unto the said ASSIGNEE, its successors, legal representatives and assigns, the entire right, title, and interest throughout the world in, to and under the said improvements, and the said application and all divisions, renewals and continuations thereof, and all Letters Patent of the United States which may be granted thereon and all reissues and extensions thereof, and all rights of priority under International Conventions and applications for Letters Patent which may hereafter be filed for said improvements in any country or countries foreign to the United States, and all Letters Patent which may be granted for said improvements in any country or countries foreign to the United States and all extensions, renewals and reissues thereof; and we hereby authorize and request the Commissioner of Patents of the United States, and any Official of any country or countries foreign to the United States, whose duty it is to issue patents on applications as aforesaid, to issue all Letters Patent for said improvements to the said ASSIGNEE, its successors, legal representatives and assigns, in accordance with the terms of this instrument.

AND WE HEREBY covenant and agree that we will communicate to the said ASSIGNEE, successors, legal representatives and assigns, any facts known to us respecting said improvements, and testify in any legal proceeding, sign all lawful papers, execute all divisional, continuing and reissue applications, make all rightful oaths and generally do everything possible to aid the said ASSIGNEE, its successors, legal representatives and assigns, to obtain and enforce proper patent protection for said improvements in all countries.

IN TESTIMONY WHEREOF, I hereunto set my hand and seal this 26th day of April, 2000

Merry R. Sherman

Merry R. Sherman, Ph.D.

STATE OF CALIFORNIA]
COUNTY OF SAN MATEO] ss.

On 4-26-2000 before me, MICHAEL MURPHY personally appeared Merry R. Sherman, Ph.D. personally known to me (or proved to me on the basis of satisfactory evidence) to be the person(s) whose name(s) is/are subscribed to the within instrument, and acknowledged to me that she executed the same in her authorized capacity(ies), and that by her signature(s) on the instrument the person(s), or the entity upon behalf of which the person(s) acted, executed the instrument.

WITNESS my hand and official seal.

[SEAL]

MICHAEL MURPHY
COMM. #1149158
NOTARY PUBLIC - CALIFORNIA
SAN MATEO COUNTY
My Comm. Expires July 29, 2001

Michael Murphy

Notary Signature

IN TESTIMONY WHEREOF, I hereunto set my hand and seal this 26 day of April, 2000

Mark Saifer
Mark G. P. Saifer, Ph.D.

STATE OF CALIFORNIA
COUNTY OF SAN MATEO
ss.

On 4/26/2000, before me, MICHAEL MURPHY, personally appeared Mark G. P. Saifer, Ph.D., personally known to me (or proved to me on the basis of satisfactory evidence) to be the person(s) whose name(s) is/are subscribed to the within instrument, and acknowledged to me that he executed the same in his authorized capacity(ies), and that by his signature(s) on the instrument the person(s), or the entity upon behalf of which the person(s) acted, executed the instrument.

WITNESS my hand and official seal.

[SEAL] MICHAEL MURPHY COMM. #1149158 NOTARY PUBLIC · CALIFORNIA SAN MATEO COUNTY My Comm. Expires July 29, 2001

Michael Murphy
Notary Signature

IN TESTIMONY WHEREOF, I hereunto set my hand and seal this 26 day of April, 2000

L. David Williams
L. David Williams, Ph.D.

STATE OF CALIFORNIA
COUNTY OF SAN MATEO
ss.

On 4/26/2000, before me, MICHAEL MURPHY, personally appeared L. David Williams personally known to me (or proved to me on the basis of satisfactory evidence) to be the person(s) whose name(s) is/are subscribed to the within instrument, and acknowledged to me that he executed the same in his authorized capacity(ies), and that by his signature(s) on the instrument the person(s), or the entity upon behalf of which the person(s) acted, executed the instrument.

WITNESS my hand and official seal.

[SEAL] MICHAEL MURPHY COMM. #1149158 NOTARY PUBLIC · CALIFORNIA SAN MATEO COUNTY My Comm. Expires July 29, 2001

Michael Murphy
Notary Signature

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PATENT ASSIGNMENT

Electronic Version v1.1
Stylesheet Version v1.1

SUBMISSION TYPE:	NEW ASSIGNMENT
NATURE OF CONVEYANCE:	ASSIGNMENT

CONVEYING PARTY DATA

Name	Execution Date
Michael S. HERSHFIELD	05/16/2006
Susan J. KELLY	05/17/2006

RECEIVING PARTY DATA

Name:	Duke University
Street Address:	Erwin Road
City:	Durham
State/Country:	NORTH CAROLINA
Postal Code:	27710

PROPERTY NUMBERS Total: 1

Property Type	Number
Patent Number:	6783965

OP $40.00 6783965

CORRESPONDENCE DATA

Fax Number: (202)371-2540
Correspondence will be sent via US Mail when the fax attempt is unsuccessful.
Phone: 202-371-2600
Email: jking@skgf.com
Correspondent Name: Steme. Kessler. Goldstein & Fox PLLC
Address Line 1: 1100 New York Avenue NW
Address Line 4: Washington, DISTRICT OF COLUMBIA 20005

ATTORNEY DOCKET NUMBER:	2057.0080000/BJD/SAC
NAME OF SUBMITTER:	Shannon A. Carroll

Total Attachments: 2
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ASSIGNMENT

In consideration of the sum of One Dollar ($1.00) or equivalent and other good and valuable consideration paid to each of the undersigned inventors: **Michael S. HERSHFIELD** and **Susan J. KELLY**, hereby sell and assign to **Duke University**, a corporation formed under the laws of North Carolina, whose mailing address is Erwin Road, Durham, NC 27710 (hereafter referred to as the Assignee), his/her entire right, title and interest, including the right to sue for past infringement and to collect for all past, present and future damages, for the United States of America (as defined in 35 U.S.C. § 100) and throughout the world,

(a) in the invention known as **Aggregate-Free Urate Oxidase for Preparation of Non-Immunogenic Polymer Conjugates** for which an application for patent in the United States of America was filed on February 10, 2000 (also known as United States Application No. 09/501,730, now U.S. Patent No. 6,783,965), in any and all applications thereon, in any and all Letters Patent(s) therefor, and

(b) in any and all applications that claim the benefit of the patent application listed above in part (a), including non-provisional applications, continuing (continuation, divisional, or continuation-in-part) applications, reissues, extensions, renewals and reexaminations of the patent application or Letters Patent therefor listed above in part (a), to the full extent of the term or terms for which Letters Patents issue, and

(c) in any and all inventions described in the patent application listed above in part (a), and in any and all forms of intellectual and industrial property protection derivable from such patent application, and that are derivable from any and all continuing applications, reissues, extensions, renewals and reexaminations of such patent application, including, without limitation, patents, applications, utility models, inventor's certificates, and designs together with the right to file applications therefor, and including the right to claim the same priority rights from any previously filed applications under the International Agreement for the Protection of Industrial Property, or any other international agreement, or the domestic laws of the country in which any such application is filed, as may be applicable;

all such rights, title and interest to be held and enjoyed by the above-named Assignee, its successors, legal representatives and assigns to the same extent as all such rights, title and interest would have been held and enjoyed by the Assignor had this assignment and sale not been made.

The undersigned inventors agree to execute all papers necessary in connection with the application(s) and any non-provisional, continuing (continuation, divisional, or continuation-in-part), reissue, reexamination or corresponding application(s) thereof and also to execute separate assignments in connection with such application(s) as the Assignee may deem necessary or expedient.

The undersigned inventors agree to execute all papers necessary in connection with any interference or patent enforcement action (judicial or otherwise) related to the application(s) or any non-provisional, continuing (continuation, divisional, or continuation-in-part), reissue or reexamination application(s) thereof and to cooperate with the Assignee in every way possible in obtaining evidence and going forward with such interference or patent enforcement action.

The undersigned inventors hereby represent that he/she has full right to convey the entire interest herein assigned, and that he/she has not executed, and will not execute, any agreement in conflict therewith.

The undersigned inventors hereby grant the patent practitioners associated with **CUSTOMER NUMBER 26111** the power to insert in this assignment any further identification that may be necessary or desirable in order to comply with the rules of the United States Patent and Trademark Office for recordation of this document.

IN WITNESS WHEREOF, executed by the undersigned inventors on the date opposite his/her name.

Date: 5/16/2006 Signature of Inventor: _____
Michael S. HERSHFIELD

Date: 5/17/2006 Signature of Inventor: _____
Susan J. KELLY

519762

EXHIBIT 2

SAVIENT
PHARMACEUTICALS, INC.

One Tower Center, 14th Floor
East Brunswick, NJ 08816

PHILIP K. YACHMETZ
Senior Vice President
General Counsel & Secretary

732-418-9300 Tel
732-565-4705 Direct
732-418-9065 Fax
pyachmetz@savientpharma.com

November 5, 2010

Commissioner for Patents
U.S. Patent and Trademark Office
Mail Stop Patent Ext.
Randolph Building
401 Dulany Street
Alexandria, VA 22314

To Whom It May Concern:

Pursuant to 35 U.S.C. 156(d)(1), Savient Pharmaceuticals, Inc. ("Savient") hereby authorizes Mountain View Pharmaceuticals, Inc. and Duke University (collectively, "the Applicants") to rely upon the marketing application activities of Savient before the U.S. Food and Drug Administration ("FDA") for the application for extension of patent term of the United States Patent No. 6,783,965 ("the '965 Patent").

Savient is the holder of marketing approval for KRYSTEXXA™, the approved product that is relevant to the application for extension of patent term of the '965 Patent. The first IND application for KRYSTEXXA™ was submitted to the FDA by Savient's predecessor – Bio-Technology General Corporation ("BTG") in 2001.

To Savient's knowledge, the Applicants are the owners of the '965 Patent. By an agreement effective on August 12, 1998, the Applicants provided BTG an

exclusive license to use the '965 Patent, including for the regulatory review of KRYSTEXXA™.

An agency relationship between the Applicants and Savient existed during the regulatory review period of KRYSTEXXA™.

Sincerely,

Philip K. Yachmetz
Senior Vice President
General Counsel & Secretary

EXHIBIT 3

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use KRYSTEXXA safely and effectively. See full prescribing information for KRYSTEXXA

KRYSTEXXA™ (pegloticase)
Injection, for intravenous infusion

Initial US Approval: 2010

WARNING: ANAPHYLAXIS and INFUSION REACTIONS
See full prescribing information for complete boxed warning.
- **Anaphylaxis and infusion reactions have been reported to occur during and after administration of KRYSTEXXA (5.1, 5.2).**
- **KRYSTEXXA should be administered in healthcare settings and by healthcare providers prepared to manage anaphylaxis and infusion reactions.**
- **Patients should be pre-medicated with antihistamines and corticosteroids.**
- **Patients should be closely monitored for an appropriate period of time for anaphylaxis after administration of KRYSTEXXA.**
- **Monitor serum uric acid levels prior to infusions and consider discontinuing treatment if levels increase to above 6 mg/dL, particularly when 2 consecutive levels above 6 mg/dL are observed.**

INDICATIONS AND USAGE

KRYSTEXXA™ (pegloticase) is a PEGylated uric acid specific enzyme indicated for the treatment of chronic gout in adult patients refractory to conventional therapy. (1)

Important Limitations of Use:
KRYSTEXXA is not recommended for the treatment of asymptomatic hyperuricemia. (1)

DOSAGE AND ADMINISTRATION

- For adult patients 8 mg given as an intravenous infusion every two weeks. (2.1)
- Do not administer as an intravenous push or bolus. (2.3)
- Monitor serum uric acid levels before each infusion. (2.3)
- Patients should be pre-medicated with antihistamines and corticosteroids. (2.3, 5.1, 5.2)
- Administer in a healthcare setting by healthcare providers prepared to manage anaphylaxis. (2.3, 5.1, 5.2)
- The KRYSTEXXA admixture should only be administered by intravenous infusion over no less than 120 minutes via gravity feed, syringe-type pump, or infusion pump. (2.3)

DOSAGE FORMS AND STRENGTHS

- 1 mL sterile concentrate for dilution containing 8 mg of pegloticase protein, expressed in uricase protein amounts. (3)

CONTRAINDICATIONS

- **Glucose-6-phosphate dehydrogenase (G6PD) Deficiency**: Before starting KRYSTEXXA, patients at higher risk for G6PD deficiency (e.g., those of African and Mediterranean ancestry) should be screened due to the risk of hemolysis and methemoglobinemia. (4)

WARNINGS AND PRECAUTIONS

- **Anaphylaxis:** Anaphylaxis occurred in patients treated with KRYSTEXXA. Anaphylaxis may occur with any infusion, including a first infusion, and generally manifests within 2 hours of the infusion. However, delayed-type hypersensitivity reactions have also been reported. KRYSTEXXA should be administered in healthcare settings and by healthcare providers prepared to manage anaphylaxis. Patients should be pre-medicated with antihistamines and corticosteroids. Patients should be closely monitored for an appropriate period of time for anaphylaxis after administration of KRYSTEXXA. (5.1)
- **Infusion Reactions**: Infusion reactions occurred in patients treated with KRYSTEXXA. KRYSTEXXA should be administered in a healthcare setting and by healthcare providers prepared to manage infusion reactions. Patients should be pre-medicated with antihistamines and corticosteroids. Monitor patients closely for signs and symptoms of infusion reactions. In the event of an infusion reaction, the infusion should be slowed, or stopped and restarted at a slower rate. If a severe infusion reaction occurs, discontinue infusion and institute treatment as needed. The risk of an infusion reaction is higher in patients who have lost therapeutic response. (5.2)
- **Gout Flares:** An increase in gout flares is frequently observed upon initiation of anti-hyperuricemic therapy, including treatment with KRYSTEXXA. If a gout flare occurs during treatment, KRYSTEXXA need not be discontinued. Gout flare prophylaxis (i.e., non-steroidal anti-inflammatory drugs [NSAID] or colchicine upon initiation of treatment) is recommended for at least the first 6 months of therapy unless medically contraindicated or not tolerated. (5.3)
- **Congestive Heart Failure**: KRYSTEXXA has not been formally studied in patients with congestive heart failure, but some patients in clinical trials experienced exacerbation. Exercise caution when using KRYSTEXXA in patients who have congestive heart failure and monitor patients closely following infusion. (5.4)

ADVERSE REACTIONS

The most common adverse reactions (occurring in at least 5% of KRYSTEXXA-treated patients) are gout flares, infusion reactions, nausea, contusion or ecchymosis, nasopharyngitis, constipation, chest pain, anaphylaxis and vomiting. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Savient Pharmaceuticals, Inc. at 1-888-579-7839 (1-888-KRYSTEXXA) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 09/2010

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: ANAPHYLAXIS AND INFUSION REACTIONS

- **Anaphylaxis and infusion reactions have been reported to occur during and after administration of KRYSTEXXA. [*see Warnings and Precautions (5.1, 5.2)*]**
- **Anaphylaxis may occur with any infusion, including a first infusion, and generally manifests within 2 hours of the infusion. However, delayed-type hypersensitivity reactions have also been reported.**
- **KRYSTEXXA should be administered in healthcare settings and by healthcare providers prepared to manage anaphylaxis and infusion reactions.**
- **Patients should be premedicated with antihistamines and corticosteroids.**
- **Patients should be closely monitored for an appropriate period of time for anaphylaxis after administration of KRYSTEXXA.**
- **Monitor serum uric acid levels prior to infusions and consider discontinuing treatment if levels increase to above 6 mg/dL, particularly when 2 consecutive levels above 6 mg/dL are observed.**

1 INDICATIONS AND USAGE

KRYSTEXXA™ (pegloticase) is a PEGylated uric acid specific enzyme indicated for the treatment of chronic gout in adult patients refractory to conventional therapy.

Gout refractory to conventional therapy occurs in patients who have failed to normalize serum uric acid and whose signs and symptoms are inadequately controlled with xanthine oxidase inhibitors at the maximum medically appropriate dose or for whom these drugs are contraindicated.

Important Limitations of Use:
KRYSTEXXA is not recommended for the treatment of asymptomatic hyperuricemia.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage

The recommended dose and regimen of KRYSTEXXA for adult patients is 8 mg (uricase protein) given as an intravenous infusion every two weeks.

The optimal treatment duration with KRYSTEXXA has not been established.

2.2 Preparation

Visually inspect KRYSTEXXA for particulate matter and discoloration before administration, whenever solution and container permit. Do not use vials if either is present. [*see Dosage Forms and Strengths (3)*]

Use appropriate aseptic technique. Withdraw 1 mL of KRYSTEXXA from the vial into a sterile syringe. Discard any unused portion of product remaining in the 2 mL vial. Inject into

a single 250 mL bag of 0.9% Sodium Chloride Injection, USP or 0.45% Sodium Chloride Injection, USP for intravenous infusion. Do not mix or dilute with other drugs.

Invert the infusion bag containing the dilute KRYSTEXXA solution a number of times to ensure thorough mixing. Do not shake.

KRYSTEXXA diluted in infusion bags is stable for 4 hours at 2° to 8°C (36° to 46°F) and at room temperature (20° to 25°C, 68° to 77°F). However it is recommended that diluted solutions be stored under refrigeration, not frozen, protected from light, and used within 4 hours of dilution. [*see How Supplied/Storage and Handling (16)*]

Before administration, allow the diluted solution of KRYSTEXXA to reach room temperature. KRYSTEXXA in a vial or in an intravenous infusion fluid should never be subjected to artificial heating (e.g., hot water, microwave).

2.3 Administration

Do not administer as an intravenous push or bolus.

Monitoring Therapy: The risk of anaphylaxis and infusion reactions is higher in patients who have lost therapeutic response. Monitor serum uric acid levels prior to infusions and consider discontinuing treatment if levels increase to above 6 mg/dL, particularly when 2 consecutive levels above 6 mg/dL are observed. [*see Warnings and Precautions (5.1, 5.2)*]

The KRYSTEXXA admixture should only be administered by intravenous infusion over no less than 120 minutes via gravity feed, syringe-type pump, or infusion pump.

Patients should receive pre-infusion medications (e.g. antihistamines, corticosteroids), to minimize the risk of anaphylaxis and infusion reactions. Administer KRYSTEXXA in a healthcare setting and by healthcare providers prepared to manage anaphylaxis and infusion reactions, and observe patients for an appropriate period of time after administration. [*see Warnings and Precautions (5.1, 5.2)*]

If an infusion reaction occurs during the administration of KRYSTEXXA, the infusion may be slowed, or stopped and restarted at a slower rate, at the discretion of the physician. Since infusion reactions can occur after completion of infusion, observation of patients for approximately an hour post-infusion should be considered. [*see Warnings and Precautions (5.2), Adverse Reactions (6.1)*]

3 DOSAGE FORMS AND STRENGTHS

KRYSTEXXA is a clear, colorless, sterile 8 mg/mL solution of pegloticase in a 2 mL single-use vial, expressed as amounts of uricase protein. KRYSTEXXA must be diluted prior to use.

4 CONTRAINDICATIONS

Glucose-6-phosphate dehydrogenase (G6PD) deficiency: KRYSTEXXA is contraindicated in patients with G6PD deficiency due to the risk of hemolysis and

methemoglobinemia. It is recommended that patients at higher risk for G6PD deficiency (e.g., patients of African or Mediterranean ancestry) be screened for G6PD deficiency before starting KRYSTEXXA.

5 WARNINGS AND PRECAUTIONS

5.1 Anaphylaxis

During pre-marketing controlled clinical trials, anaphylaxis was reported with a frequency of 6.5% of patients treated with KRYSTEXXA every 2 weeks, compared to none with placebo. Manifestations included wheezing, peri-oral or lingual edema, or hemodynamic instability, with or without rash or urticaria. Cases occurred in patients being pre-treated with one or more doses of an oral antihistamine, an intravenous corticosteroid and/or acetaminophen. This pre-treatment may have blunted or obscured symptoms or signs of anaphylaxis and therefore the reported frequency may be an underestimate. [*See Adverse Reactions (6)*]

KRYSTEXXA should be administered in a healthcare setting by healthcare providers prepared to manage anaphylaxis. Patients should be pre-treated with antihistamines and corticosteroids. Anaphylaxis may occur with any infusion, including a first infusion, and generally manifests within 2 hours of the infusion. However, delayed type hypersensitivity reactions have also been reported. Patients should be closely monitored for an appropriate period of time for anaphylaxis after administration of KRYSTEXXA. Patients should be informed of the symptoms and signs of anaphylaxis and instructed to seek immediate medical care should anaphylaxis occur after discharge from the healthcare setting.

The risk of anaphylaxis is higher in patients whose uric acid level increases to above 6 mg/dL, particularly when 2 consecutive levels above 6 mg/dL are observed. Monitor serum uric acid levels prior to infusions and consider discontinuing treatment if levels increase to above 6 mg/dL.

5.2 Infusion Reactions

During pre-marketing controlled clinical trials, infusion reactions were reported in 26% of patients treated with KRYSTEXXA 8 mg every 2 weeks, and 41% of patients treated with KRYSTEXXA 8 mg every 4 weeks, compared to 5% of patients treated with placebo. These infusion reactions occurred in patients being pre-treated with an oral antihistamine, intravenous corticosteroid and/or acetaminophen. This pre-treatment may have blunted or obscured symptoms or signs of infusion reactions and therefore the reported frequency may be an underestimate. [*See Adverse Reactions (6)*]

KRYSTEXXA should be administered in a healthcare setting by healthcare providers prepared to manage infusion reactions. Patients should be pre-treated with antihistamines and corticosteroids. KRYSTEXXA should be infused slowly over no less than 120 minutes. In the event of an infusion reaction, the infusion should be slowed, or stopped and restarted at a slower rate.

The risk of infusion reaction is higher in patients whose uric acid level increases to above 6 mg/dL, particularly when 2 consecutive levels above 6 mg/dL are observed. Monitor serum

uric acid levels prior to infusions and consider discontinuing treatment if levels increase to above 6 mg/dL.

5.3 Gout Flares

Gout flares may occur after initiation of KRYSTEXXA. [*see Adverse Reactions (6.1)*] An increase in gout flares is frequently observed upon initiation of anti-hyperuricemic therapy, due to changing serum uric acid levels resulting in mobilization of urate from tissue deposits. Gout flare prophylaxis with a non-steroidal anti-inflammatory drug (NSAID) or colchicine is recommended starting at least 1 week before initiation of KRYSTEXXA therapy and lasting at least 6 months, unless medically contraindicated or not tolerated. KRYSTEXXA does not need to be discontinued because of a gout flare. The gout flare should be managed concurrently as appropriate for the individual patient. [*see Dosage and Administration (2))*]

5.4 Congestive Heart Failure

KRYSTEXXA has not been formally studied in patients with congestive heart failure, but some patients in the clinical trials experienced exacerbation. [*see Adverse Reactions (6.1)*] Exercise caution when using KRYSTEXXA in patients who have congestive heart failure and monitor patients closely following infusion.

5.5 Re-treatment with KRYSTEXXA

No controlled trial data are available on the safety and efficacy of re-treatment with KRYSTEXXA after stopping treatment for longer than 4 weeks. Due to the immunogenicity of KRYSTEXXA, patients receiving re-treatment may be at increased risk of anaphylaxis and infusion reactions. Therefore, patients receiving re-treatment after a drug-free interval should be monitored carefully. [*see Adverse Reactions (6.2)*]

6 ADVERSE REACTIONS

The most commonly reported serious adverse reactions from pre-marketing controlled clinical trials were anaphylaxis, which occurred at a frequency of 6.5% in patients treated with KRYSTEXXA 8 mg every 2 weeks, compared to none with placebo; infusion reactions, which occurred at a frequency of 26% in patients treated with KRYSTEXXA 8 mg every 2 weeks, compared to 5% treated with placebo; and gout flares, which were more common during the first 3 months of treatment with KRYSTEXXA compared with placebo. All patients in pre-marketing controlled clinical trials were pre-treated with an oral antihistamine, intravenous corticosteroid and/or acetaminophen to prevent anaphylaxis and infusion reaction. Patients also received non-steroidal anti-inflammatory drugs or colchicine, or both, for at least 7 days as gout flare prophylaxis before beginning KRYSTEXXA treatment. [*see Boxed Warning, Warnings and Precautions (5.1, 5.2, 5.3)*]

6.1 Clinical Trials Experience

The data described below reflect exposure to KRYSTEXXA in patients with chronic gout refractory to conventional therapy in two replicate randomized, placebo-controlled, double-blind 6-month clinical trials: 85 patients were treated with KRYSTEXXA 8 mg every 2 weeks; 84 patients were treated with KRYSTEXXA 8 mg every 4 weeks; and 43 patients were treated with placebo. These patients were between the ages of 23 and 89 years (average

55 years); 173 patients were male and 39 were female; and 143 patients were White/Caucasian, 27 were Black/African American, 24 were Hispanic/Latino and 18 were all other ethnicities. Common co-morbid conditions among the enrolled patients included hypertension (72%), dyslipidemia (49%), chronic kidney disease (28%), diabetes (24%), coronary artery disease (18%), arrhythmia (16%), and cardiac failure/left ventricular dysfunction (12%).

Because clinical studies are conducted under widely varying and controlled conditions, adverse reaction rates observed in clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug, and may not predict the rates observed in a broader patient population in clinical practice.

Anaphylaxis:
Diagnostic criteria of anaphylaxis were skin or mucosal tissue involvement, and, either airway compromise, and/or reduced blood pressure with or without associated symptoms, and a temporal relationship to KRYSTEXXA or placebo injection with no other identifiable cause. Using these clinical criteria, anaphylaxis was identified in 14 (5.1%) of 273 total patients studied in the clinical program of IV KRYSTEXXA. The frequency was 6.5% for the every 2-week dosing regimen (8 of 123 patients), and 4.8% for the 4-week dosing frequency (6 of 126) of KRYSTEXXA. There were no cases of anaphylaxis in patients receiving placebo. Anaphylaxis generally occurred within 2 hours after treatment. This occurred with patients being pre-treated with an oral antihistamine, intravenous corticosteroid, and acetaminophen. [see *Boxed Warning, Warnings and Precautions (5.1, 5.2)*]

Infusion Reactions:
Infusion reactions occurred in 26% of patients in the 2 week dosing regimen group and 41% of patients in the 4 week dosing regimen group, compared to 5% of placebo-treated patients. Manifestations of these reactions included urticaria (frequency of 10.6%), dyspnea (frequency of 7.1%), chest discomfort (frequency of 9.5%), chest pain (frequency of 9.5%), erythema (frequency of 9.5%), and pruritus (frequency of 9.5%). These manifestations overlap with the symptoms of anaphylaxis, but in a given patient did not occur together to satisfy the clinical criteria for diagnosing anaphylaxis. Infusion reactions are thought to result from release of various mediators, such as cytokines. Infusion reactions occurred at any time during a course of treatment with approximately 3% occurring with the first infusion, and approximately 91% occurred during the time of infusion. Some infusion reaction manifestations were reduced with slowing the rate of infusion, or stopping the infusion and restarting the infusion at a slower rate. These infusion reactions occurred with all patients being pre-treated with an oral antihistamine, intravenous corticosteroid and acetaminophen. [*see Boxed Warning, Warnings and Precautions (5.1, 5.2)*]

Gout Flares:
Gout flares were common in the study patients before randomization to treatment, with patients experiencing an average of 10 flares in the preceding 18 months prior to study entry. During the controlled treatment period with KRYSTEXXA or placebo, the frequencies of gout flares were high in all treatment groups, but more so with KRYSTEXXA treatment

during the first 3 months of treatment, which seemed to decrease in the subsequent 3 months of treatment. The percentages of patients with any flare for the first 3 months were 74%, 81%, and 51%, for KRYSTEXXA 8 mg every 2 weeks, KRYSTEXXA 8 mg every 4 weeks, and placebo, respectively. The percentages of patients with any flare for the subsequent 3 months were 41%, 57%, and 67%, for KRYSTEXXA 8 mg every 2 weeks, KRYSTEXXA 8 mg every 4 weeks, and placebo, respectively. Patients received gout flare prophylaxis with colchicine and/or nonsteroidal anti-inflammatory drugs (NSAIDs) starting at least one week before receiving KRYSTEXXA. [*see Warnings and Precautions (5.3)*]

Congestive Heart Failure:

Two cases of congestive heart failure exacerbation occurred during the trials in patients receiving treatment with KRYSTEXXA 8 mg every 2 weeks. No cases were reported in placebo-treated patients. Four subjects had exacerbations of pre-existing congestive heart failure while receiving KRYSTEXXA 8 mg every 2 weeks during the open-label extension study. [*see Warnings and Precautions (5.4)*].

Other Adverse Reactions:

The most commonly reported adverse reactions that occurred in greater than or equal to 5% of patients treated with KRYSTEXXA 8mg every 2 weeks are provided in Table 1.

Table 1. Adverse Reactions Occurring in 5% or More of Patients Treated with KRYSTEXXA Compared to Placebo

Adverse Reaction (Preferred Term)	KRYSTEXXA 8 mg every 2 weeks (N=85) N[a] (%)	Placebo (N=43) N (%)
Gout flare	65 (77%)	35 (81%)
Infusion reaction	22 (26%)	2 (5%)
Nausea	10 (12%)	1 (2%)
Contusion[b] or Ecchymosis[b]	9 (11%)	2 (5%)
Nasopharyngitis	6 (7%)	1 (2%)
Constipation	5 (6%)	2 (5%)
Chest Pain	5 (6%)	1 (2%)
Anaphylaxis	4 (5%)	0 (0%)
Vomiting	4 (5%)	1 (2%)

[a] If the same subject in a given group had more than one occurrence in the same preferred term event category, the subject was counted only once.

[b] Most did not occur on the day of infusion and could be related to other factors (e.g. concomitant medications relevant to contusion or ecchymosis, insulin dependent diabetes mellitus).

6.2 Immunogenicity

Anti-pegloticase antibodies developed in 92% of patients treated with KRYSTEXXA every 2 weeks, and 28% for placebo. Anti-PEG antibodies were also detected in 42% of patients treated with KRYSTEXXA. High anti-pegloticase antibody titer was associated with a failure

to maintain pegloticase-induced normalization of uric acid. The impact of anti-PEG antibodies on patients' responses to other PEG-containing therapeutics is unknown.

There was a higher incidence of infusion reactions in patients with high anti-pegloticase antibody titer: 53% (16 of 30) in the KRYSTEXXA every 2 weeks group compared to 6% in patients who had undetectable or low antibody titers.

As with all therapeutic proteins, there is a potential for immunogenicity. The observed incidence of antibody positivity in an assay is highly dependent on several factors including assay sensitivity and specificity and assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, the comparison of the incidence of antibodies to pegloticase with the incidence of antibodies to other products may be misleading.

7 DRUG INTERACTIONS

No studies of interactions of KRYSTEXXA with other drugs have been conducted. Because anti-pegloticase antibodies appear to bind to the PEG portion of the drug, there may be potential for binding with other PEGylated products. The impact of anti-PEG antibodies on patients' responses to other PEG-containing therapeutics is unknown.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

A complete evaluation of the reproductive and developmental toxicity of pegloticase has not been completed. Adequate animal reproduction studies have not been conducted with KRYSTEXXA. It is not known whether KRYSTEXXA can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. There are no adequate and well-controlled studies in pregnant women. KRYSTEXXA should be used during pregnancy only if clearly needed.

Pegloticase was not teratogenic in rats administered 0, 5, 10, or 40 mg/kg twice weekly by the intravenous route on gestation days 6 through 16 (the doses are approximately 6-fold to 50-fold higher than the maximum recommended human dose (MRHD) of 8 mg (0.133 mg/kg (based on a 60 kg person) every 2 weeks based on a mg/m^2 comparison).

8.3 Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, it is not recommended to administer KRYSTEXXA to a nursing mother.

8.4 Pediatric Use

The safety and effectiveness of KRYSTEXXA in pediatric patients less than 18 years of age have not been established.

8.5 Geriatric Use

Of the total number of patients treated with KRYSTEXXA 8 mg every 2 weeks in the controlled studies, 34% (29 of 85) were 65 years of age and older and 12% (10 of 85) were 75 years of age and older. No overall differences in safety or effectiveness were observed between older and younger patients, but greater sensitivity of some older individuals cannot be ruled out. No dose adjustment is needed for patients 65 years of age and older.

8.6 Renal Impairment

No dose adjustment is required for patients with renal impairment. A total of 32% (27 of 85) of patients treated with KRYSTEXXA 8 mg every 2 weeks had a creatinine clearance of ≤62.5 mL/min. No overall differences in efficacy were observed.

10 OVERDOSAGE

No reports of overdosage with KRYSTEXXA have been reported. The maximum dose that has been administered as a single intravenous dose is 12 mg as uricase protein.

Patients suspected of receiving an overdose should be monitored, and general supportive measures should be initiated as no specific antidote has been identified.

11 DESCRIPTION

KRYSTEXXA (pegloticase) is a uric acid specific enzyme which is a PEGylated product that consists of recombinant modified mammalian urate oxidase (uricase) produced by a genetically modified strain of *Escherichia coli*. Uricase is covalently conjugated to monomethoxypoly(ethylene glycol) [mPEG] (10 kDa molecular weight). The cDNA coding for uricase is based on mammalian sequences. Each uricase subunit has a molecular weight of approximately 34 kDa per subunit. The average molecular weight of pegloticase (tetrameric enzyme conjugated to mPEG) is approximately 540 kDa.

KRYSTEXXA is intended for intravenous infusion.

KRYSTEXXA is a sterile, clear, colorless solution containing 8 mg/mL pegloticase in phosphate-buffered saline.

KRYSTEXXA (pegloticase) concentrations are expressed as concentrations of uricase protein. Each mL of KRYSTEXXA contains 8 mg of uricase protein (conjugated to 24 mg of 10 kDa mPEG), 2.18 mg Disodium Hydrogen Phosphate Dihydrate ($Na_2HPO_4 \bullet 2H_2O$), 8.77 mg Sodium Chloride (NaCl), 0.43 mg Sodium Dihydrogen Phosphate Dihydrate ($NaH_2PO_4 \bullet 2H_2O$), and Water for Injection to deliver 8 mg of pegloticase (as uricase protein).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

KRYSTEXXA is a uric acid specific enzyme which is a recombinant uricase and achieves its therapeutic effect by catalyzing the oxidation of uric acid to allantoin, thereby lowering serum uric acid. Allantoin is an inert and water soluble purine metabolite. It is readily eliminated, primarily by renal excretion.

12.2 Pharmacodynamics

Approximately 24 hours following the first dose of KRYSTEXXA, mean plasma uric acid levels for subjects in the KRYSTEXXA groups were 0.7 mg/dL for the KRYSTEXXA 8 mg every 2 weeks group. In comparison, the mean plasma uric acid level for the placebo group was 8.2 mg/dL.

In a single-dose, dose-ranging trial, following 1-hour intravenous infusions of 0.5, 1, 2, 4, 8 or 12 mg of pegloticase in 24 patients with symptomatic gout (n=4 subjects/dose group), plasma uric acid decreased with increasing pegloticase dose or concentrations. The duration of suppression of plasma uric acid appeared to be positively associated with pegloticase dose. Sustained decrease in plasma uric acid below the solubility concentration of 6 mg/dL for more than 300 hours was observed with doses of 8 mg and 12 mg.

12.3 Pharmacokinetics

Pegloticase levels were determined in serum based on measurements of uricase enzyme activity.

Following single intravenous infusions of 0.5 mg to 12 mg pegloticase in 23 patients with symptomatic gout, maximum serum concentrations of pegloticase increased in proportion to the dose administered.

The population pharmacokinetic analysis showed that age, sex, weight, and creatinine clearance did not influence the pharmacokinetics of pegloticase. Significant covariates included in the model for determining clearance and volume of distribution were found to be body surface area and anti-pegloticase antibodies.

The pharmacokinetics of pegloticase has not been studied in children and adolescents.

No formal studies were conducted to examine the effects of either renal or hepatic impairment on pegloticase pharmacokinetics.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies have not been performed to evaluate the carcinogenic potential of pegloticase.

The genotoxic potential of pegloticase has not been evaluated.

Fertility studies in animals have not been performed.

13.2 Animal Toxicology and/or Pharmacology

In a 12-week intravenous repeat-dose study in dogs, there was a dose-dependent increase in vacuolated macrophages in the spleen. The presence of vacuolated macrophages likely reflects accumulated removal of injected pegloticase (foreign) material from the circulation. There was no evidence of degeneration, inflammation, or necrosis associated with the

vacuoles findings, however there was evidence of decreased functional response to liposaccharides.

In a 39-week, repeat dose dog study, there was a dose dependent increase in vacuolated cells in several organs, including the spleen, adrenal gland, liver, heart, duodenum and jejunum. In the spleen, liver, duodenum and jejunum, these vacuoles were within macrophages and most likely represented phagocytic removal of pegloticase from the circulation. However, the vacuolated cells in the heart and adrenal gland did not stain as macrophages. In the aortic outflow tract of the heart, vacuoles were in the cytoplasm of endothelial cells in the intimal lining of the aorta. In the adrenal gland, vacuoles were located within cortical cells in the zona reticularis and zona fasciculata. The clinical significance of these findings and the functional consequences are unknown.

14 CLINICAL STUDIES

The efficacy of KRYSTEXXA was studied in adult patients with chronic gout refractory to conventional therapy in two replicate, multicenter, randomized, double-blind, placebo-controlled studies of six months duration: Trial 1 and Trial 2. Patients were randomized to receive KRYSTEXXA 8 mg every 2 weeks or every 4 weeks or placebo in a 2:2:1 ratio. Studies were stratified for the presence of tophi. Seventy-one percent (71%) of patients had baseline tophi. All patients were prophylaxed with an oral antihistamine, intravenous corticosteroid and acetaminophen. Patients also received prophylaxis for gout flares with non-steroidal anti-inflammatory drugs (NSAIDs) or colchicine, or both, beginning at least one week before KRYSTEXXA treatment unless medically contraindicated or not tolerated. Patients who completed the randomized clinical trials were eligible to enroll in a 2-year open label extension study.

Entry criteria for patients to be eligible for the trials were: baseline serum uric acid (SUA) of at least 8 mg/dL; had symptomatic gout with at least 3 gout flares in the previous 18 months or at least 1 gout tophus or gouty arthritis; and had a self-reported medical contraindication to allopurinol or medical history of failure to normalize uric acid (to less than 6 mg/dL) with at least 3 months of allopurinol treatment at the maximum medically appropriate dose.

The mean age of study subjects was 55 years (23-89); 82% were male, mean body mass index (BMI) was 33 kg/m^2, mean duration of gout was 15 years, and mean baseline SUA was 10 mg/dL.

To assess the efficacy of KRYSTEXXA in lowering uric acid, the primary endpoint in both trials was the proportion of patients who achieved plasma uric acid (PUA) less than 6 mg/dL for at least 80% of the time during Month 3 and Month 6. As shown in Table 2, a greater proportion of patients treated with KRYSTEXXA every 2 weeks achieved urate lowering to below 6 mg/dL than patients receiving placebo. Although the 4 week regimen also demonstrated efficacy for the primary endpoint, this regimen was associated with increased frequency of anaphylaxis and infusion reactions and less efficacy with respect to tophi.

Table 2 Plasma Uric Acid < 6 mg/dL for at Least 80% of the Time During Months 3 and 6

Treatment Group	N	Number (%) of Subjects Who Met Response Criteria	95% Confidence Interval[1]	P-Value[2]
Trial 1				
Pegloticase 8 mg every 2 weeks	43	20 (47%)	[32%, 61%]	<0.001
Pegloticase 8 mg every 4 weeks	41	8 (20%)	[7%, 32%]	0.044
Placebo	20	0 (0%)		
Trial 2				
Pegloticase 8 mg every 2 weeks	42	16 (38%)	[23%, 53%]	<0.001
Pegloticase 8 mg every 4 weeks	43	21 (49%)	[34%, 64%]	<0.001
Placebo	23	0 (0%)		

[1] 95% confidence interval for differences in responder rate between pegloticase group vs. placebo
[2] P-value using Fisher's exact test to compare pegloticase group vs. placebo
Note: Based on post-hoc analyses of the clinical trial data, if KRYSTEXXA had been stopped when a patient's uric acid level rose to greater than 6 mg/dL on a single occasion, the incidence of infusion reactions would have been reduced by approximately 67%, but the success rates for the primary efficacy endpoint would have been reduced by approximately 20%. If KRYSTEXXA had been stopped after 2 consecutive uric acid levels greater than 6 mg/dL, the incidence of infusion reactions would have been half, and there would have been little change in the efficacy outcome.

The effect of treatment on tophi was a secondary efficacy endpoint and was assessed using standardized digital photography, image analysis, and a Central Reader blinded to treatment assignment. Approximately 70% of patients had tophi at baseline. A pooled analysis of data from Trial 1 and Trial 2 was performed as pre-specified in the protocols. At Month 6, the percentage of patients who achieved a complete response (defined as 100% resolution of at least one target tophus, no new tophi appear and no single tophus showing progression) was 45%, 26%, and 8%, with KRYSTEXXA 8 mg every 2 weeks, KRYSTEXXA 8 mg every 4 weeks, and placebo, respectively. The difference between KRYSTEXXA and placebo was statistically significant for the every 2 week dosing regimen, but not for the every 4 week dosing regimen.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

KRYSTEXXA is supplied as a clear, colorless, sterile solution in phosphate buffered saline intended for intravenous infusion after dilution. KRYSTEXXA is supplied in a single-use 2 mL glass vial with a Teflon® coated (latex-free) rubber injection stopper to deliver KRYSTEXXA as 8 mg of uricase protein in 1 mL volume.

Storage and Handling

Before the preparation for use, KRYSTEXXA must be stored in the carton and maintained at all times under refrigeration between 2° to 8°C (36° to 46°F). **Protect from light. Do not shake or freeze.**

Do not use beyond the expiration date stamped.

NDC# 54396-801-01

17 PATIENT COUNSELING INFORMATION

See Medication Guide

17.1 General Information

Provide and instruct patients to read the accompanying Medication Guide before starting treatment and before each subsequent treatment.

17.2 Anaphylaxis and Infusion Reactions

- Anaphylaxis and infusion reactions can occur at any infusion while on therapy. Counsel patients on the importance of adhering to any prescribed medications to help prevent or lessen the severity of these reactions.
- Educate patients on the signs and symptoms of anaphylaxis, including wheezing, peri-oral or lingual edema, hemodynamic instability, and rash or urticaria.
- Educate patients on the most common signs and symptoms of an infusion reaction, including urticaria (skin rash), erythema (redness of the skin), dyspnea (difficulty breathing), flushing, chest discomfort, chest pain, and rash.
- Advise patients to seek medical care immediately if they experience any symptoms of an allergic reaction during or at any time after the infusion of KRYSTEXXA. [*see Warnings and Precautions (5.1, 5.2), Adverse Reactions (6.1)*]

17.3 Glucose-6-phosphate dehydrogenase (G6PD) Deficiency

Inform patients not to take KRYSTEXXA if they have a condition known as G6PD deficiency. Explain to patients that G6PD deficiency is more frequently found in individuals of African or Mediterranean ancestry and that they may be tested to determine if they have G6PD deficiency, unless already known. [*See Contraindications (4)*]

17.4 Gout Flares

Explain to patients that gout flares may initially increase when starting treatment with KRYSTEXXA, and that medications to help reduce flares may need to be taken regularly for the first few months after KRYSTEXXA is started. [*see Warnings and Precautions (5.3), Adverse Reactions (6.1)*] Advise patients that they should not stop KRYSTEXXA therapy if they have a flare.

Manufactured by:
Savient Pharmaceuticals, Inc.
One Tower Center, 14th Floor
East Brunswick, NJ 08816

EXHIBIT 4

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Our STN: BL 125293/0

BLA APPROVAL
September 14, 2010

Savient Pharmaceuticals, Inc.
One Tower Center, 14th Floor
East Brunswick, NJ 08816

Attention: Steve Hamburger, Ph.D.
Group Vice President, Quality and Regulatory Affairs

Dear Dr. Hamburger:

Please refer to your Biologics License Application (BLA) dated and received October 31, 2008, submitted under section 351 of the Public Health Service Act for Krystexxa (pegloticase) Injection, for intravenous infusion.

We acknowledge receipt of your amendments dated November 14 and December 5, 9, 22, and 30, 2008, January 16 and 28, February 4, 6, and 27, March 10 and 19, April 3, 8, 21, 22, and 29, May 12, June 11, 18, 22, 23, 25, and 26, and July 9, 10, and 17, 2009, and March 15, April 23, June 1, 7, and 16, July 2 and 28, August 4, and September 2 (2) 3, 8(2), 9 and 14, 2010.

The March 15, 2010, submission constituted a complete response to our July 31, 2009, action letter.

We are issuing Department of Health and Human Services U.S. License No. 1801 to Savient Pharmaceuticals, East Brunswick, New Jersey, under the provisions of section 351(a) of the Public Health Service Act controlling the manufacture and sale of biological products. The license authorizes you to introduce into, or deliver for introduction into, interstate commerce those products for which your company has demonstrated compliance with establishment and product standards.

Under this license, you are authorized to manufacture the product pegloticase. Pegloticase is indicated for the treatment of chronic gout in adult patients refractory to conventional therapy.

Under this license, you are approved to manufacture pegloticase drug substance at BTG, Ltd., in Kiryat Malachi, Israel. The final formulated product will be manufactured, filled, labeled, and packaged at Enzon Pharmaceuticals, Inc., Indianapolis, Indiana. You may label your product with the proprietary name Krystexxa and market it in vials containing 32 mg of pegloticase corresponding to 8 mg uricase protein conjugated to 24 mg of 10 kDa mPEG.

The dating period for pegloticase shall be 24 months (2 years) from the date of manufacture when stored at 4° to 8°C. The date of manufacture shall be defined as the date of final sterile filtration of the formulated drug product. The dating period for your drug substance shall be 6 months when stored at 2° to 8°C. The dating period for the uricase intermediate shall be 54 days when stored at 2° to 8°C.

You are not currently required to submit samples of future lots of pegloticase to the Center for Drug Evaluation and Research (CDER) for release by the Director, CDER, under 21 CFR 610.2. We will continue to monitor compliance with 21 CFR 610.1, requiring completion of tests for conformity with standards applicable to each product prior to release of each lot.

Any changes in the manufacturing, testing, packaging, or labeling of pegloticase, or in the manufacturing facilities, will require the submission of information to your biologics license application for our review and written approval, consistent with 21 CFR 601.12.

We are approving this application for use as recommended in the enclosed agreed-upon labeling text.

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 601.14(b)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the enclosed labeling and Medication Guide. Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As* available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf. For administrative purposes, designate this submission **"Product Correspondence – Final SPL for approved BLA STN 125293/0."**

The SPL will be accessible via publicly available labeling repositories.

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

CARTON AND IMMEDIATE-CONTAINER LABELS

Submit final printed carton and immediate-container labels that are identical to the enclosed carton and container labels as soon as they are available, but no more than 30 days after they are printed. Submit these labels electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications*

and Related Submissions Using the eCTD Specifications. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Product Correspondence – Final Printed Carton and Container Labels for approved BLA STN 125293/0.**" Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with final printed labeling (FPL) that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product has an orphan drug designation for this indication, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess known serious risks of severe infusion reactions, anaphylaxis, and immune complex-related adverse events, as well as to identify unexpected risks related to fertility, pre-, peri-, and post-natal development, and cytoplasmic vacuoles in the adrenal gland and the aortic outflow tract of the heart.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

1. An observational safety study enrolling 500 patients treated with Krystexxa (pegloticase) for one year duration. Patients enrolled should have hyperuricemia and gout and be refractory to standard uric acid-lowering therapies (e.g., allopurinol). The study should include the following objectives:

a. An evaluation of the frequency and severity of infusion reactions, anaphylaxis, and immune complex-related adverse events.

b. Identification of serious adverse events associated with Krystexxa (pegloticase) therapy.

The timetable you submitted on September 14, 2010, states that you will conduct this study according to the following schedule:

Final Protocol Submission: February 2011
Study Completion Date: July 2015
Final Report Submission: December 2015

2. Conduct a male and female fertility study in rats per ICH-S5A and ICH-S5B.

The timetable you submitted on September 14, 2010, states that you will conduct this study according to the following schedule:

Final Protocol Submission: January 2011
Study Completion Date: November 2011
Final Report Submission: June 2012

3. Conduct an embryo-fetal development study in the rabbit model (Segment 2) according to ICH-S5A guidance.

The timetable you submitted on September 14, 2010, states that you will conduct this study according to the following schedule:

Final Protocol Submission (Main Study): September 2011
Study Completion (Main Study): March 2012
Final Report Submission (Main Study): September 2012

4. Conduct a peri-natal and post-natal development study in the rat model (Segment 3)

The timetable you submitted on September 14, 2010, states that you will conduct this study according to the following schedule:

Final Protocol Submission: January 2011
Study Completion: February 2012
Final Report Submission: October 2012

5. Conduct an 18-month study in dogs to evaluate the impact of cytoplasmic vacuoles in the adrenal gland and the aortic outflow tract of the heart.

The timetable you submitted on September 14, 2010, states that you will conduct this study according to the following schedule:

Final Protocol Submission: May 2011
Study Completion Date: November 2012
Final Report Submission: July 2013

6. The current anti-PEG antibody ELISA shows a very high degree of intra-and inter-assay variability possibly related to the PEG coating of the ELISA plate. This indicates either that the assay is not sufficiently optimized or that the format is unsuitable. Redevelop the anti-PEG antibody assay to address these concerns.

   Final Report Submission: April 2011

7. The sensitivity of your IgE assay, as currently designed, is insufficient to detect IgE antibodies to the product. For an antigen-specific IgE assay to be useful, it should have sensitivity in the nanogram to sub-nanogram range, and there are technologies currently available that can meet this criterion. Develop a more sensitive antigen-specific IgE assay. Consider using ECL technology.

   Final Report Submission: October 2012

8. Your IgE assay was not properly validated due to a lack of positive control antibody. Develop a suitable positive control for the IgE ELISA. Cross-linking the current rabbit polyclonal to a human IgE may be an option.

   Final Report Submission: January 2012

Submit the protocols to your IND 010122, with a cross-reference letter to this BLA 125293. Submit all final reports to your BLA 125293. Prominently identify the submissions with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

- **REQUIRED POSTMARKETING PROTOCOL UNDER 505(o)**
- **REQUIRED POSTMARKETING FINAL REPORT UNDER 505(o)**
- **REQUIRED POSTMARKETING CORRESPONDENCE UNDER 505(o)**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 601.70, requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 601.70 to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 601.70. We remind you that to comply with

505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments in your submission dated September 14, 2010. These commitments are listed below.

9. Revise the acceptance criteria for the peptide map assay used to quantify Krystexxa lysine site occupancy with PEG molecules, to specify a numerical range for all the polypeptides identified. Submit the new acceptance criteria for the assay.

   Final Report Submission: September 2012

10. Conduct a study to evaluate the sensitivity of the LC-MS Peptide Mapping Assay to detect over- and under-pegylated uricase molecules and submit the results.

    Final Report Submission: January 2011

11. Reevaluate the release criteria for the following assays. Submit the revised acceptance criteria and supporting data for the drug substance and drug product after 30 lots of Krystexxa (pegloticase) are manufactured.

    a. Enzymatic activity
    b. Km and k_{cat} determination by product accumulation and substrate depletion
    c. Monomer and HMW forms by SEC-HPLC Abs_{220}
    d. Monomer HMW and LMW forms by Abs_{214}

    Final Report Submission (for release acceptance criteria): Sept 2012

12. Reevaluate the stability acceptance criteria for the following assays. Submit the revised criteria and supporting data for the drug substance and drug product after 30 lots of Krystexxa (pegloticase) are manufactured.

    a. Enzymatic activity assay
    b. Km and k_{cat} determination by product accumulation and substrate depletion assay
    c. Monomer and HMW forms by SEC-HPLC Abs_{220} assay
    d. Monomer HMW and LMW forms by Abs_{214} assay.

    Final Report Submission (for stability acceptance criteria): June 2013

13. Develop and implement an enzymatic assay, based on product accumulation that determines K_m and k_{cat} values for release of uricase intermediate and submit the new specification and supporting data.

Validation Report Completion: June 2011
Final Report Submission (Acceptance Criteria): December 2012

14. Include stress conditions in the annual stability program for drug substance and drug product. Submit the revised stability protocols.

Final Protocol Submission: January 2011

15. Evaluate in-use stability of the drug product by assessing the impact dilution of 1.0 mL drug product (pH 7.0) into 250 mL saline solution with the worst case scenario pH (4.5) has on the final pH of the infusion solution. Submit the results of the study and risk mitigation strategies if the final pH is below 6.2.

Study Completion Date: April 2011
Final Report Submission: July 2011

16. Provide the results of aseptic fill validation and results of stability studies on three batches of Krystexxa (pegloticase) held for at least six months to support the reduction of the drug product vial overfill to that recommended in the USP.

Final Protocol Submission: November 2010
Study Completion Date: March 2011
Final Report Submission: January 2012

Submit clinical protocols to your IND 010122 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final reports to this BLA 125293. In addition, under 21 CFR 601.70 you should include a status summary of each commitment in your annual progress report of postmarketing studies to this BLA 125293. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled **"Postmarketing Commitment Protocol," "Postmarketing Commitment Final Report,"** or **"Postmarketing Commitment Correspondence."**

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)). The details of the REMS requirements were outlined in our complete response letter dated July 31, 2009.

Your proposed REMS, submitted on September 14, 2010, and appended to this letter, is approved. The REMS consists of a Medication Guide, a communication plan, and a timetable for submission of assessments of the REMS.

The REMS assessment plan should include but is not limited to the following:

a. An evaluation of the patients' and prescribers' understanding of the serious risks of Krystexxa (pegloticase).

b. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24.

c. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance with 21 CFR 208.24.

d. Specification of measures that would be taken to increase awareness if surveys of healthcare providers indicate that provider awareness is not adequate.

e. Summaries of adverse event reporting of infusion reactions, including an analysis of anaphylaxis, and whether appropriate therapy was instituted.

f. With regard to the communication plan:

1. The dates of product launch and the launch of the communication plan
2. The date(s) of mailing and number of recipients of the Dear Healthcare Provider letter (DHCP) and the Dear Infusion Site Medical Personnel letter (DISMP).
3. The number of mailings returned.
4. The sources of the recipient lists.
   The dates of the annual meetings attended and number of materials distributed.
5. The names of the journals that published the journal information piece and the dates of publication.

Assessments of an approved REMS must also include, under section 505-1(g)(3)(B) and (C), information on the status of any post approval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. With respect to any such post approval study, you must include the status of such study, including whether any difficulties completing the study have been encountered. With respect to any such post approval clinical trial, you must include the status of such clinical trial, including whether enrollment has begun, the number of participants enrolled, the expected completion date, whether any difficulties completing the clinical trial have been encountered, and registration information with respect to requirements under subsections (i) and (j) of section 402 of the Public Health Service Act. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 601.70 and including any updates to the status information since the annual report was prepared. Failure to comply with the REMS assessment provisions in section 505-1(g) could result in enforcement action.

We remind you that in addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of FDCA.

Prominently identify the submission containing the REMS assessments or proposed modifications with the following wording in bold, capital letters at the top of the first page of the submission:

BLA 125293
REMS ASSESSMENT

NEW SUPPLEMENT FOR BLA 125293
PROPOSED REMS MODIFICATION
REMS ASSESSMENT

NEW SUPPLEMENT (NEW INDICATION FOR USE) FOR BLA 125293
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

If you do not submit electronically, please send five copies of REMS-related submissions.

REPORTING REQUIREMENTS

You must submit adverse experience reports under the adverse experience reporting requirements for licensed biological products (21 CFR 600.80). You should submit postmarketing adverse experience reports to:

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Prominently identify all adverse experience reports as described in 21 CFR 600.80.

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

You must submit distribution reports under the distribution reporting requirements for licensed biological products (21 CFR 600.81).

You must submit reports of biological product deviations under 21 CFR 600.14. You should promptly identify and investigate all manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding, and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA-3486 to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
5901-B Ammendale Road
Beltsville, MD 20705-1266

Biological product deviations, sent by courier or overnight mail, should be addressed to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
10903 New Hampshire Avenue, Bldg. 51, Room 4206
Silver Spring, MD 20992-0002

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

All promotional claims must be consistent with and not contrary to approved labeling. You should not make a comparative promotional claim or claim of superiority over other products unless you have substantial evidence to support that claim.

LETTERS TO HEALTH CARE PROFESSIONALS

If you decide to issue a letter communicating important safety-related information about this drug product (e.g., a "Dear Health Care Professional" letter), we request that you submit, at least 24 hours prior to issuing the letter, an electronic copy of the letter to this BLA, to CDERMedWatchSafetyAlerts@fda.hhs.gov, and to the following address:

MedWatch Program
Office of Special Health Issues
Food and Drug Administration
10903 New Hampshire Ave
Building 32, Mail Stop 5353
Silver Spring, MD 20993

POST-ACTION FEEDBACK MEETING

New molecular entities and new biologics qualify for a post-action feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, call Ramani Sista, Regulatory Project Manager, at (301) 796-1236.

Sincerely,

/Curtis J. Rosebraugh, M.D., M.P.H./
Curtis J. Rosebraugh, M.D., M.P.H.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosures:
Package Insert with Medication Guide
REMS documents
Carton and Container Labels

EXHIBIT 5

US006783965B1

(12) **United States Patent**
Sherman et al.

(10) **Patent No.: US 6,783,965 B1**
(45) **Date of Patent: *Aug. 31, 2004**

(54) **AGGREGATE-FREE URATE OXIDASE FOR PREPARATION OF NON-IMMUNOGENIC POLYMER CONJUGATES**

(75) Inventors: **Merry R. Sherman**, San Carlos, CA (US); **Mark G. P. Saifer**, San Carlos, CA (US); **L. David Williams**, Fremont, CA (US)

(73) Assignee: **Mountain View Pharmaceuticals, Inc.**, Menlo Park, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **09/501,730**

(22) Filed: **Feb. 10, 2000**

(51) **Int. Cl.**[7] **C12N 9/04**; C12N 15/00; A61K 38/44; C07K 1/00; C07H 21/04

(52) **U.S. Cl.** **435/190**; 435/191; 435/440; 424/94.4; 536/23.2; 530/350

(58) **Field of Search** 435/190, 191, 435/440, 170; 424/94.4, 94.6; 536/23.2; 530/350, 413

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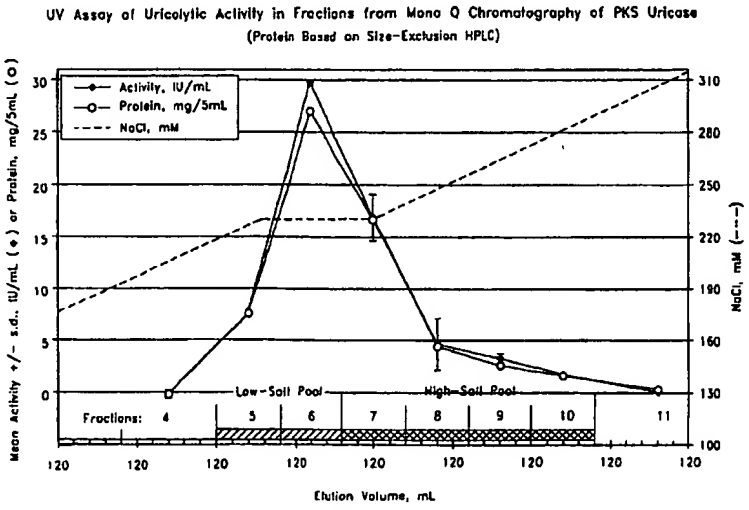
Primary Examiner—Ponnathapu Achutamurthy
Assistant Examiner—Yong Pak
(74) *Attorney, Agent, or Firm*—Sterne, Kessler, Goldstein & Fox P.L.L.C.

(57) **ABSTRACT**

A naturally occurring or recombinant protein, especially a mutein of porcine urate oxidase (uricase), that is essentially free of large aggregates can be rendered substantially non-immunogenic by conjugation with a sufficiently small number of strands of polymer such that the bioactivity of the protein is essentially retained in the conjugate. Such conjugates are unusually well suited for treatment of chronic conditions because they are less likely to induce the formation of antibodies and/or accelerated clearance than are similar conjugates prepared from protein preparations containing traces of large aggregates.

30 Claims, 6 Drawing Sheets



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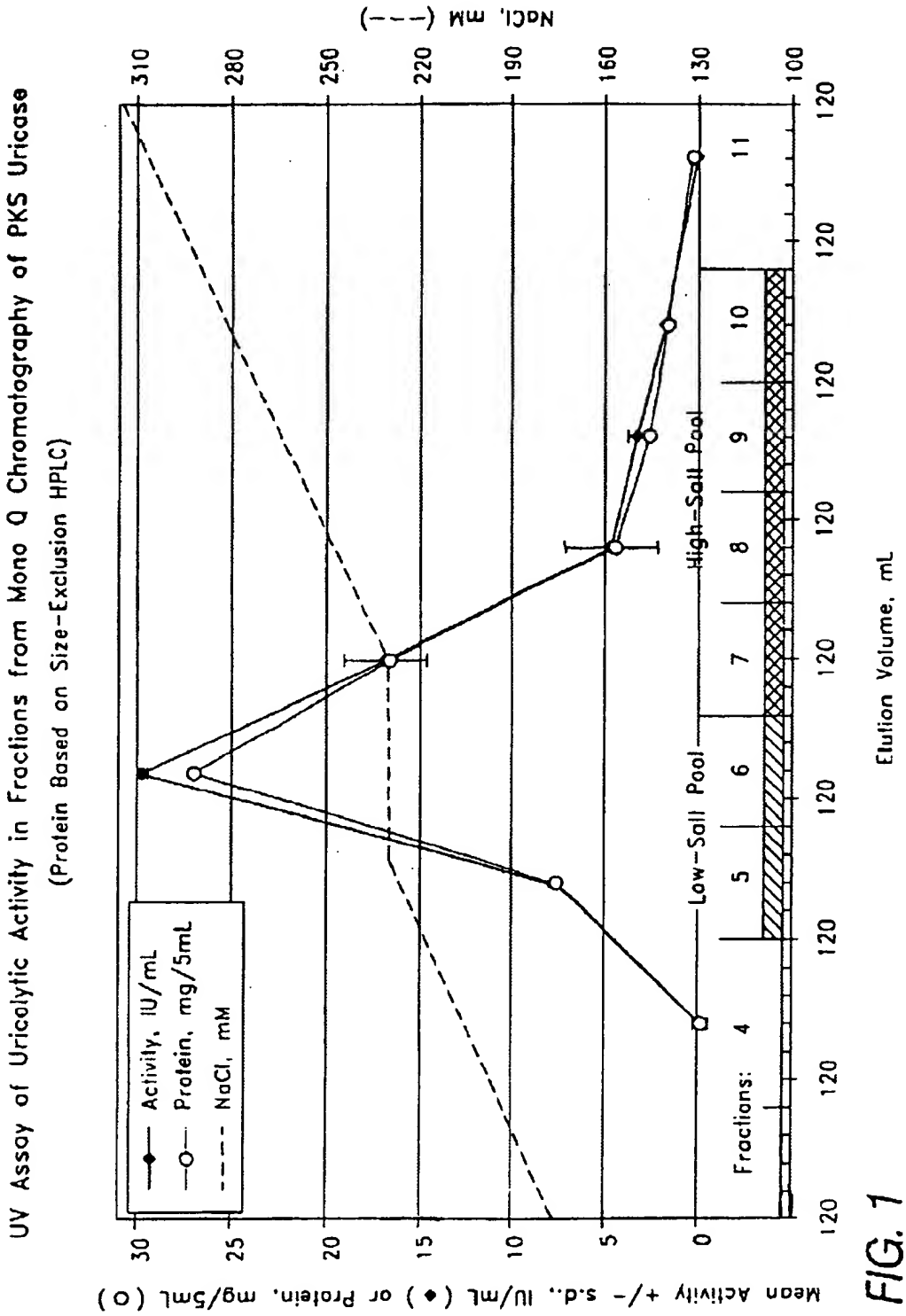
UV Assay of Uricolytic Activity in Fractions from Mono Q Chromatography of PKS Uricase
(Protein Based on Size-Exclusion HPLC)
Activity, IU/mL
Protein, mg/5mL
NaCl, mM
Mean Activity +/- s.d., IU/mL (◆) or Protein, mg/5mL (○)
NaCl, mM (---)
Low-Salt Pool
High-Salt Pool
Fractions: 4 5 6 7 8 9 10 11
Elution Volume, mL

FIG. 1

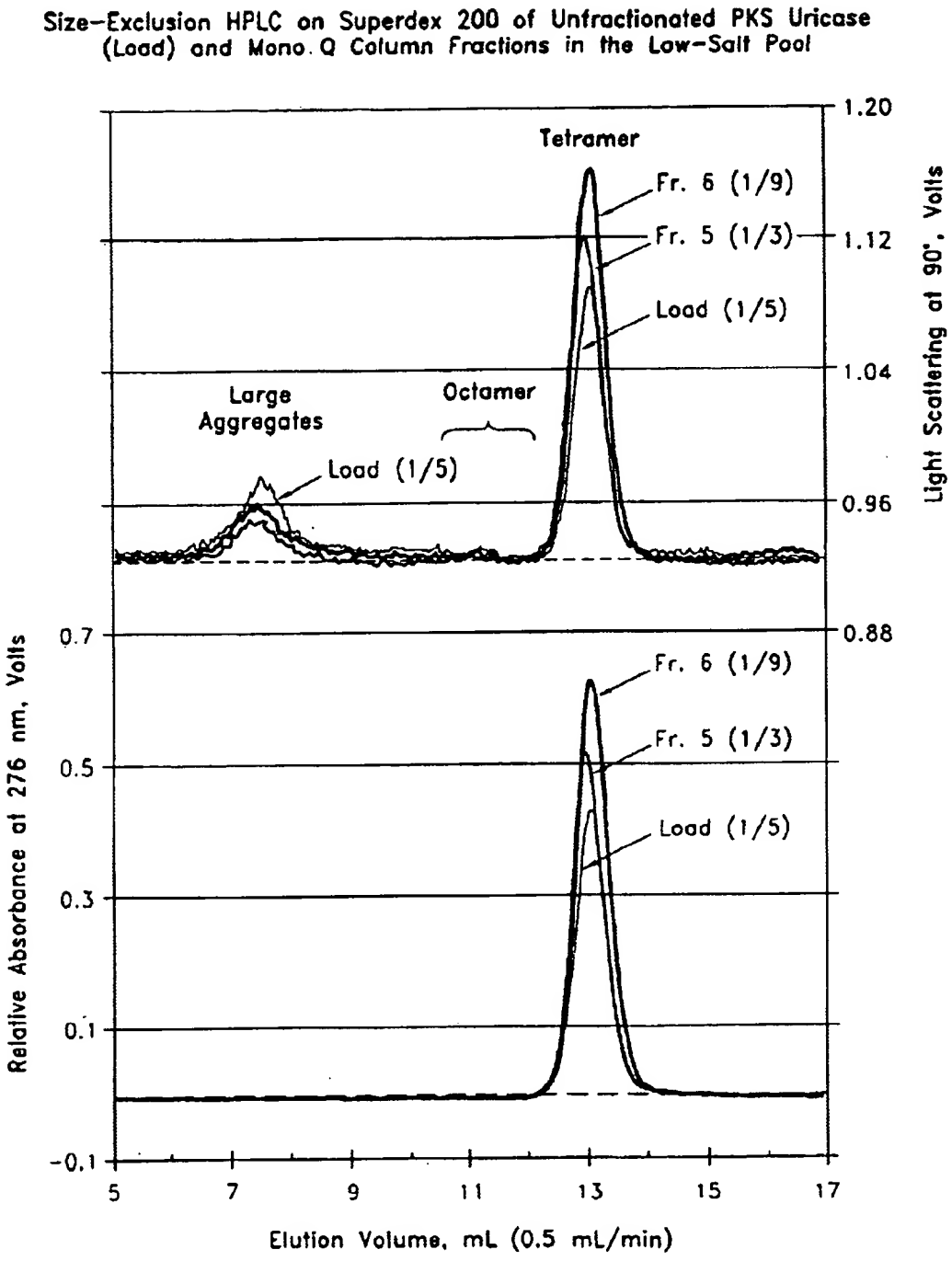
Size-Exclusion HPLC on Superdex 200 of Unfractionated PKS Uricase (Load) and Mono Q Column Fractions in the Low-Salt Pool
Tetramer
Fr. 6 (1/9)
Fr. 5 (1/3)
Load (1/5)
Large Aggregates
Octamer
Load (1/5)
Fr. 6 (1/9)
Fr. 5 (1/3)
Load (1/5)
Relative Absorbance at 276 nm, Volts
Light Scattering at 90°, Volts
0.7
0.5
0.3
0.1
-0.1
1.20
1.12
1.04
0.96
0.88
5
7
9
11
13
15
17
Elution Volume, mL (0.5 mL/min)

FIG. 2

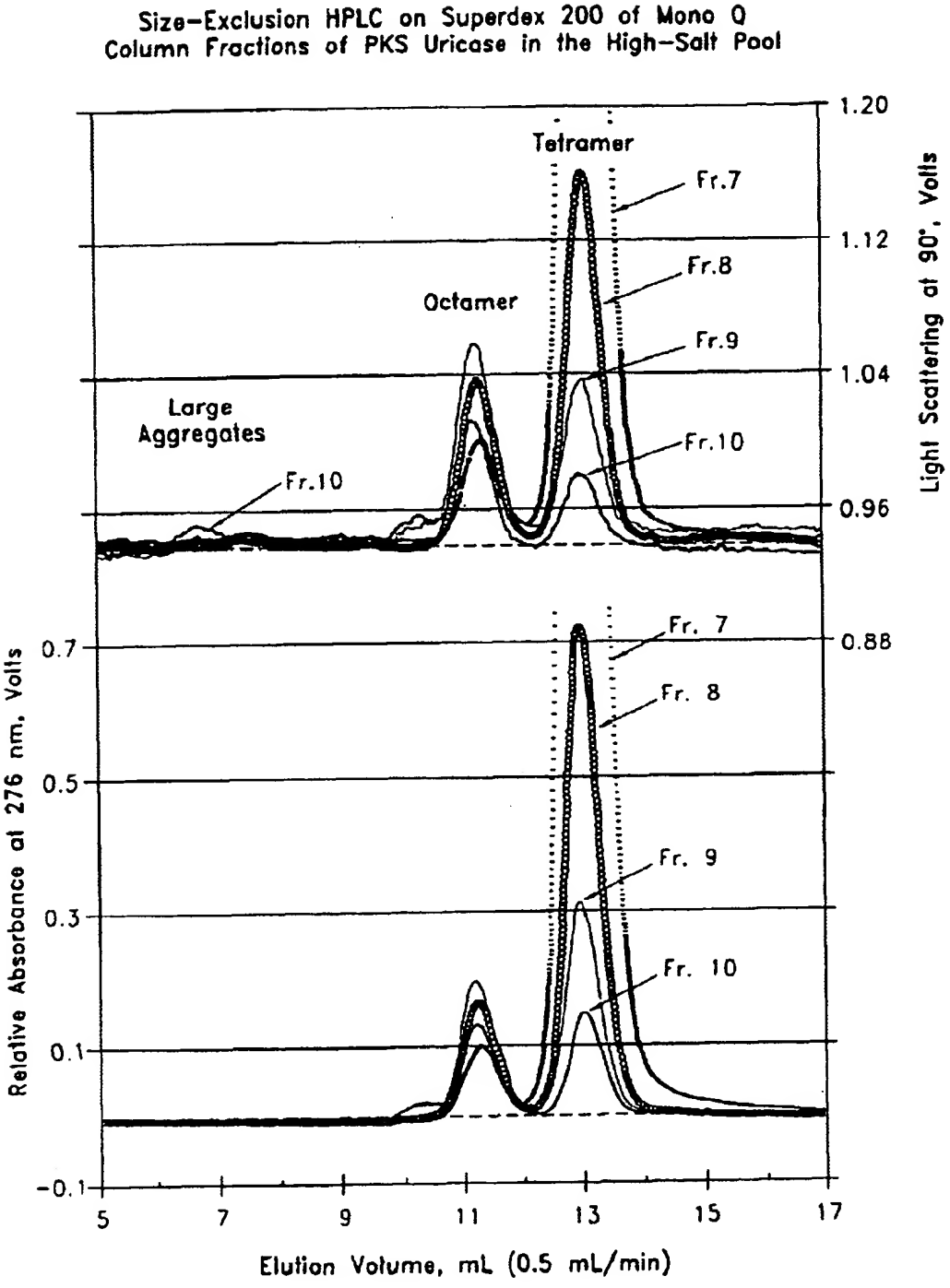
Size-Exclusion HPLC on Superdex 200 of Mono Q
Column Fractions of PKS Uricase in the High-Salt Pool
Tetramer
Octamer
Large
Aggregates
Fr.7
Fr.8
Fr.9
Fr.10
Fr.10
Fr. 7
Fr. 8
Fr. 9
Fr. 10
1.20
1.12
1.04
0.96
0.88
Light Scattering at 90°, Volts
0.7
0.5
0.3
0.1
-0.1
Relative Absorbance at 276 nm, Volts
5
7
9
11
13
15
17
Elution Volume, mL (0.5 mL/min)

FIG. 3

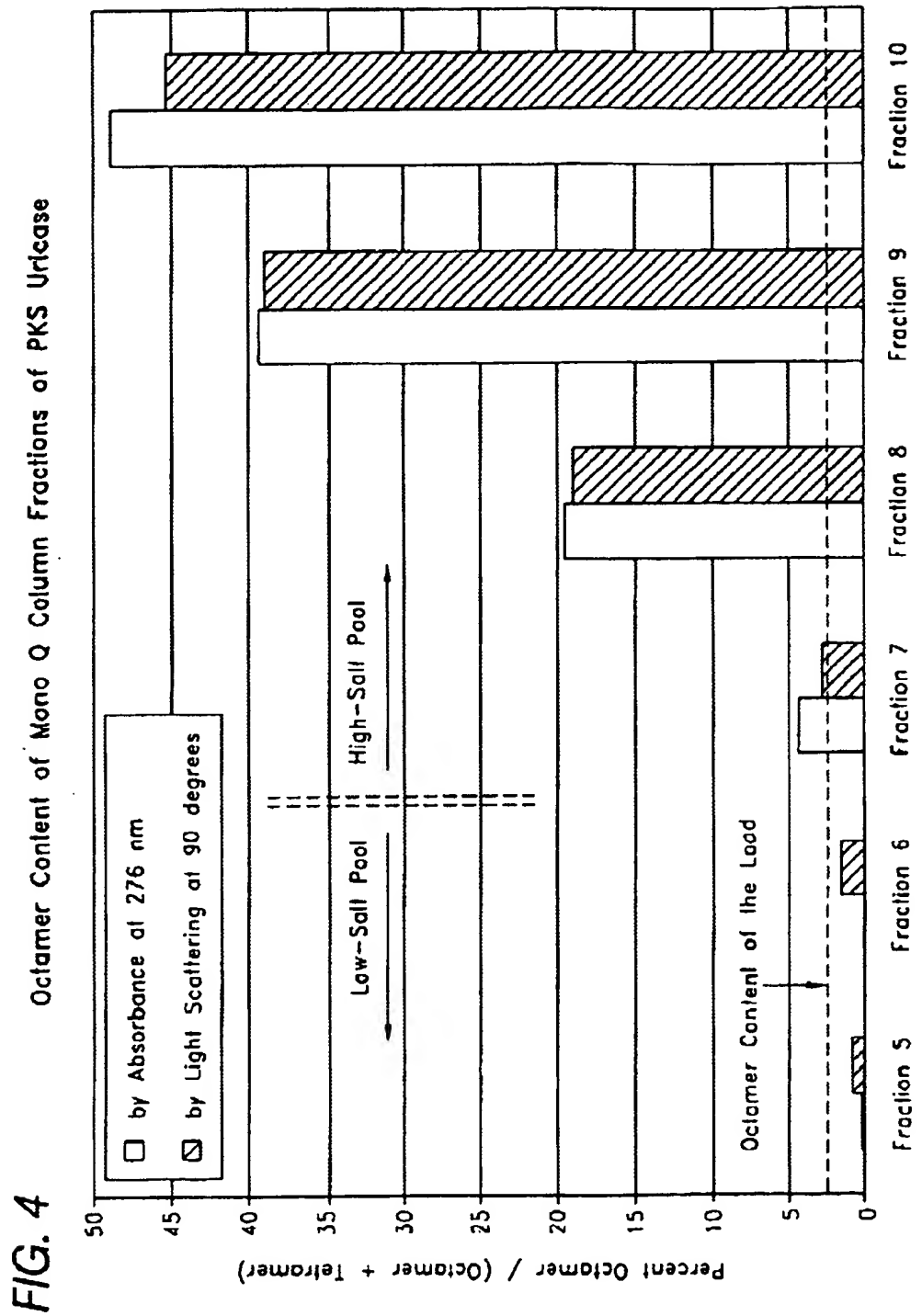
Octamer Content of Mono Q Column Fractions of PKS Urease
by Absorbance at 276 nm
by Light Scattering at 90 degrees
Low-Salt Pool
High-Salt Pool
Octamer Content of the Load
Percent Octamer / (Octamer + Tetramer)
50
45
40
35
30
25
20
15
10
5
0
Fraction 5
Fraction 6
Fraction 7
Fraction 8
Fraction 9
Fraction 10

FIG. 4

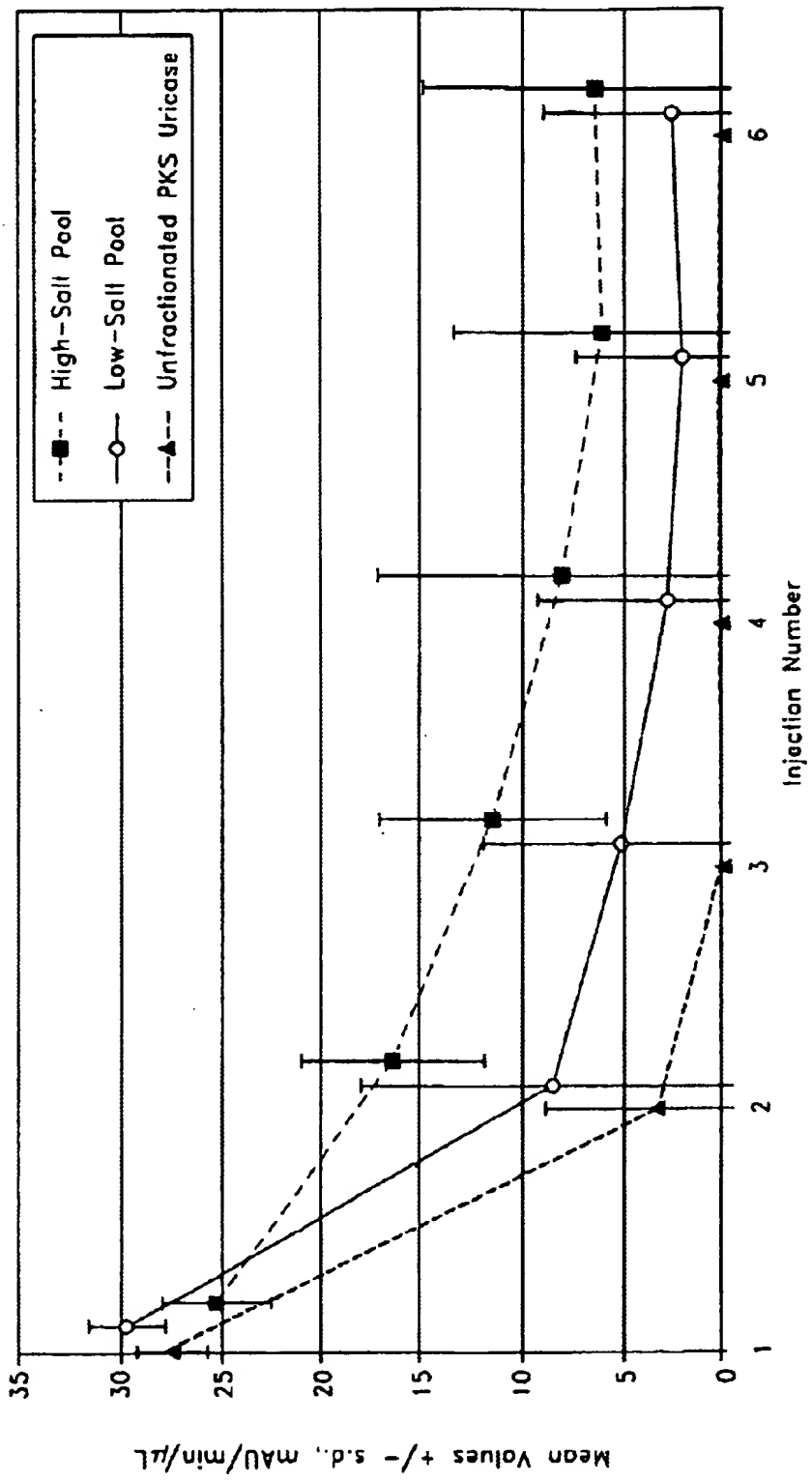
UV Uricase Assays of Sera from Mice Injected with 6 x 10-kDa PEG Conjugates of PKS Uricase or of Pools from Mono Q Column Fractions
(Mice Were Bled 24 Hours after Each Weekly Injection.)
High-Salt Pool
Low-Salt Pool
Unfractionated PKS Uricase
Mean Values +/- s.d., mAU/min/μL
Injection Number
0
5
10
15
20
25
30
35
1
2
3
4
5
6

FIG. 5

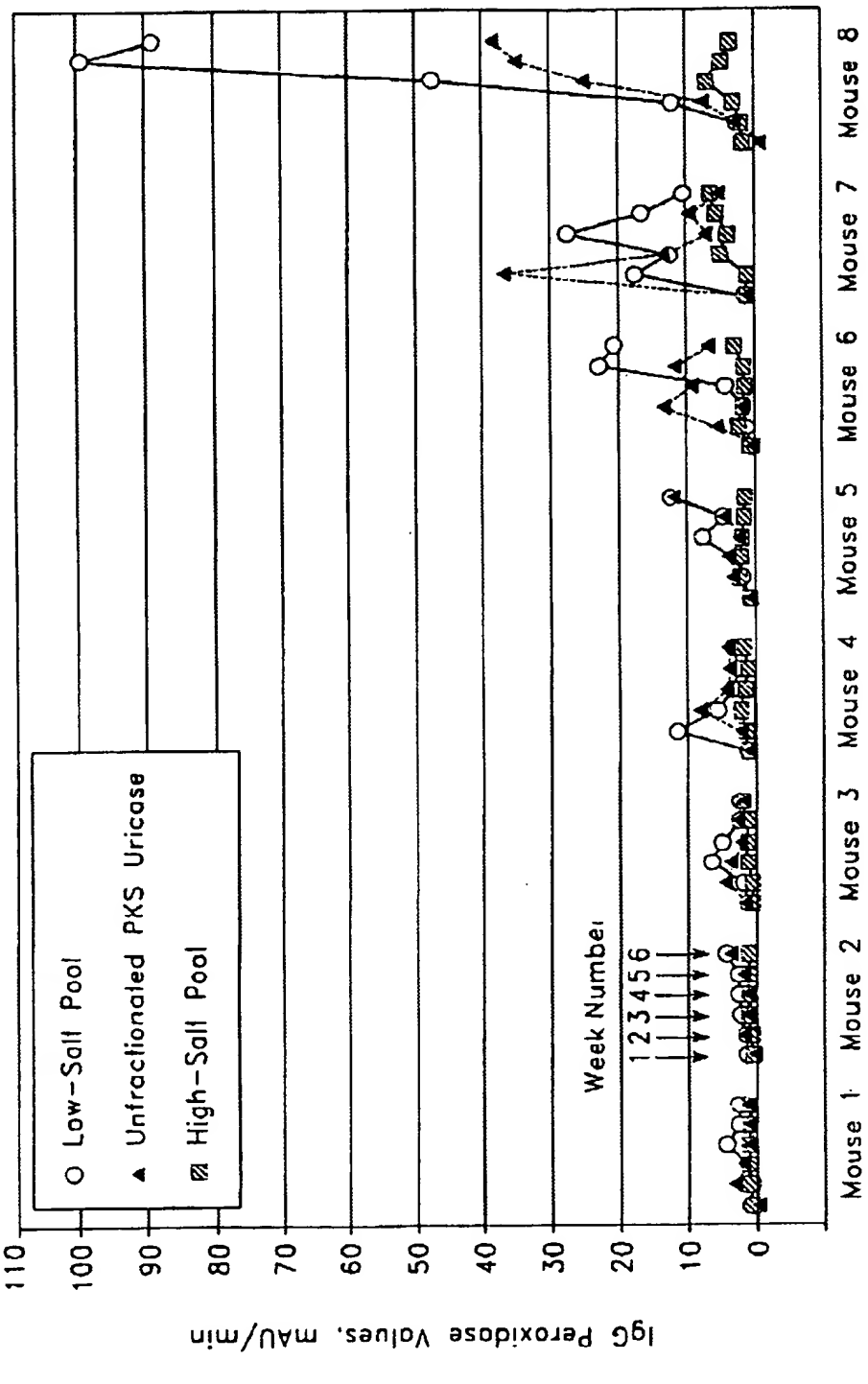
6x10-kDa PEG Conjugates of PKS Uricase:
Unfractionated and Low-Salt or High-Salt Pools
O Low-Salt Pool
▲ Unfractionated PKS Uricase
▨ High-Salt Pool
Week Number
1 2 3 4 5 6
lgG Peroxidase Values, mAU/min
110
100
90
80
70
60
50
40
30
20
10
0
Mouse 1
Mouse 2
Mouse 3
Mouse 4
Mouse 5
Mouse 6
Mouse 7
Mouse 8

FIG. 6

AGGREGATE-FREE URATE OXIDASE FOR PREPARATION OF NON-IMMUNOGENIC POLYMER CONJUGATES

STATEMENT OF GOVERNMENT RIGHTS IN THE INVENTION

A portion of the research described in this application was made with support from the U.S.-Israel Binational Industrial Research and Development Foundation. Accordingly, the U.S. Government may have certain rights in the invention.

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to purification and chemical modification of proteins to prolong their circulating lifetimes and reduce their immunogenicity. More specifically, the invention relates to the removal of aggregates larger than octamers from urate oxidases (uricases) prior to conjugation of poly(ethylene glycols) or poly(ethylene oxides). This substantially eliminates uricase immunogenicity without compromising its uricolytic activity.

2. Description of the Related Art

Statements contained in this background section do not constitute an admission of prior art, but instead reflect the inventors' own subjective comments on and interpretations of the state of the art at the time the invention was made. These interpretations may include personal, heretofore undisclosed, insights of the inventors, which insights were not themselves part of the prior art.

Urate oxidases (uricases; E.C. 1.7.3.3) are enzymes that catalyze the oxidation of uric acid to a more soluble product, allantoin, a purine metabolite that is more readily excreted. Humans do not produce enzymatically active uricase, as a result of several mutations in the gene for uricase acquired during the evolution of higher primates. Wu, X, et al., (1992) *J Mol Evol* 34:78–84. As a consequence, in susceptible individuals, excessive concentrations of uric acid in the blood (hyperuricemia) and in the urine (hyperuricosuria) can lead to painful arthritis (gout), disfiguring urate deposits (tophi) and renal failure. In some affected individuals, available drugs such as allopurinol (an inhibitor of uric acid synthesis) produce treatment-limiting adverse effects or do not relieve these conditions adequately. Hande, K R, et al., (1984) *Am J Med* 76:4–56; Fam, A G, (1990) *Baillière's Clin Rheumatol* 4:177–192. Injections of uricase can decrease hyperuricemia and hyperuricosuria, at least transiently. Since uricase is a foreign protein in humans, however, even the first injection of the unmodified protein from *Aspergillus flavus* has induced anaphylactic reactions in several percent of treated patients (Pui, C-H, et al., (1997) *Leukemia* 11:1813–1816), and immunologic responses limit its utility for chronic or intermittent treatment. Donadio, D, et al., (1981) *Nouv Presse Méd* 10:711–712; Leaustic, M, et al., (1983) *Rev Rhum Mal Osteoartic* 50:553–554.

U.S. patent application Ser. No. 09/370,084 and published International Application No. PCT/US99/17514, the entire contents of which are incorporated herein by reference, disclose poly (ethylene glycol)-urate oxidase (PEG-uricase) that retains at least about 75% of the uricolytic activity of unconjugated uricase and has substantially reduced immunogenicity. In one such purified uricase, each subunit is covalently linked to an average of 2 to 10 strands of PEG, wherein each molecule of PEG may have a molecular weight between about 5 kDa and 100 kDa.

The aggregation of proteins is known to increase their immunogenicity. This understanding has contributed to the development of methods for intentionally aggregating proteins by treatments such as thermal denaturation and cross-linking by exposure to glutaraldehyde prior to use in the preparation of vaccines or for immunization of animals to produce antisera.

Unintentional aggregation of proteins has also been recognized as contributing to immunization or sensitization during clinical use of therapeutic proteins, e.g. for human gamma globulin (Henney et al. (1968) *N. Engl. J Med.* 278:2244–2246) and for human growth hormone (Moore et al. (1980) *J Clin. Endocrinol. Metab.* 51:691–697). The contribution of aggregates to the immunogenicity of human interferon alpha has been demonstrated in BALB/c mice (Braun et al. (1997) *Pharm. Res.* 14:1472–1478) and an enzyme-linked immunosorbent assay (ELISA) has been developed for their measurement (Braun et al. (1997) *Pharm. Res.* 14:1394–1400).

In contrast to the known effects of aggregation on the immunogenicity of proteins, there are not reports of the effect of aggregation on the immunogenicity of proteins conjugated to poly(alkylene glycols) such as PEG. There is a need for poly(alkylene glycol)-uricase conjugates that substantially eliminates uricase immunogenicity without compromising its uricolytic activity. The present invention provide such compositions.

SUMMARY OF THE INVENTION

Conjugation of proteins with poly(alkylene glycols), especially PEG, produces conjugates with reduced immunogenicity and increased persistence in the bloodstream. In attempting to produce substantially non-immunogenic conjugates of uricase that retain substantially all of the uricolytic activity of the unmodified uricase preparation, it was discovered that traces of large aggregates of uricase in the starting material were surprisingly effective at provoking both antibody formation and accelerated clearance from the circulation, both of which are deleterious, after repeated injections of PEG conjugates prepared from uricase containing such aggregates. Surprisingly, the present inventors found that the increased immunogenicity and accelerated clearance were not due to the presence of well-defined, moderate-sized aggregates of the uricase subunit that are larger than the native tetramer, e.g. aggregates containing eight subunits (octamers). The octameric form of uricase is present at sufficiently high concentrations in most preparations of uricase to be detectable by its absorbance of UV light, e.g. at 214 nm or 276 nm, or by its contribution to the refractive index or other measurements of protein concentration. Nevertheless, the octamers themselves were found to contribute minimally to the immunogenicity and accelerated clearance of PEG-uricase conjugates, in contrast with the much smaller quantities of the much larger aggregates that are undetectable by UV absorbance under the conditions tested but are readily detected by static (Raleigh) or dynamic light scattering. Therefore, the removal of such traces of very large aggregates prior to conjugation with PEG was found to decrease the immunogenicity and the accelerated clearance of the resultant PEG-uricase conjugates to a surprising extent.

One embodiment of the present invention is purified urate oxidase (uricase) substantially free of aggregates larger than octamers. Preferably, the uricase is mammalian uricase. More preferably, the uricase is porcine liver, bovine liver or ovine liver uricase. In one aspect of this preferred embodiment, the uricase is recombinant. In another aspect of this preferred embodiment, the uricase has substantially the

sequence of porcine, bovine, ovine or baboon liver uricase. Advantageously, the uricase is chimeric. Preferably, the uricase is PKS uricase. In another aspect of this preferred embodiment, the uricase has substantially the sequence of baboon liver uricase in which tyrosine 97 has been replace by histidine. Preferably, the uricase comprises an amino terminus and a carboxy terminus, and wherein the uricase is truncated at one terminus or both termini. Advantageously, the uricase is a fungal or microbial uricase. Preferably, the fungal or microbial uricase is isolated from *Aspergillus flavus, Arthrobacter globiformis*, Bacillus sp. or *Candida utilis*, or is a recombinant enzyme having substantially the sequence of one of said uricases. Alternatively, the uricase is an invertebrate uricase. Preferably, the invertebrate uricase is isolated from *Drosophila melanoguster* or *Drosophila pseudoobscura*, or is a recombinant enzyme having substantially the sequence of one of said uricases. In another aspect of this preferred embodiment, the uricase is a plant uricase. Preferably, the plant uricase is isolated from root nodules of *Glycine max* or is a recombinant enzyme having substantially the sequence of the uricase.

In one aspect of this preferred embodiment, the uricase described above is conjugated to poly(ethylene glycol) or poly(ethylene oxide), under conditions such that the uricase in the conjugate is substantially free of aggregates larger than octamers. Preferably, the uricase is conjugated to poly(ethylene glycol) or poly(ethylene oxide) via a urethane (carbamate), secondary amine or amide linkage. In one aspect of this preferred embodiment, the poly(ethylene glycol) is monomethoxy poly(ethylene glycol). In another aspect of this preferred embodiment, the poly(ethylene glycol) or poly(ethylene oxide) has a molecular weight between about 5 kDa and 30 kDa. Preferably, the poly (ethylene glycol) or poly(ethylene oxide) has a molecular weight between about 10 kDa and 20 kDa. Advantageously, the average number of strands of said poly(ethylene glycol) or poly(ethylene oxide) is between about 2 and 12 per uricase subunit. More advantageously, the average number of strands of said poly(ethylene glycol) or poly(ethylene oxide) is between about 6 and 10 per uricase subunit. Most advantageously, the average number of strands of said poly(ethylene glycol) or poly(ethylene oxide) is between about 7 and 9 per uricase subunit. Preferably, the poly (ethylene glycol) or poly(ethylene oxide) is linear. Alternatively, the poly(ethylene glycol) or poly(ethylene oxide) is branched.

The present invention also provides a pharmaceutical composition for lowering uric acid levels in a body fluid or tissue, comprising the uricase conjugate described above and a pharmaceutically acceptable carrier. Preferably, the composition is stabilized by lyophilization and dissolves upon reconstitution to provide solutions suitable for parenteral administration.

Another embodiment of the invention is a method for purifying uricase having reduced immunogenicity, comprising the step of separating uricase aggregates larger than octamers in uricase fractions, and excluding such aggregates from the purified uricase. Preferably, the separating step comprises the step of detecting aggregates larger than octamers from at least a portion of the uricase fractions and excluding the fractions containing the aggregates. Advantageously, the detecting step comprises measurement of light scattering.

The present invention also provides isolated uricase prepared by the method described above.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** illustrates uricase activity, total protein and salt concentrations in fractions from a Pharmacia Biotech Mono Q (1×10 cm) anion exchange column. Uricase activity was measured at room temperature by monitoring the decrease in absorbance at 292 nm of 100 μM uric acid in 200 mM sodium borate, pH 9.2. Total protein was determined from the area under the curve of the absorbance peak of uricase in size-exclusion HPLC analyses. Salt concentrations were calculated from the conductivities at room temperature using a standard curve for NaCl in the same buffer.

FIG. **2** illustrates size-exclusion HPLC analysis on a Pharmacia Superdex 200 column (1×30 cm) of the load and selected fractions from a preparative Mono Q chromatography of porcine uricase containing the mutations R291K and T301S (PKS uricase) showing data obtained by a light-scattering detector at 90° C. (upper curves) and by absorbance at 276 nm (lower curves). The different signal strengths of the tetrameric, octameric and more highly aggregated forms of uricase in the unfractionated sample (load) and the various fractions are evident. The load was diluted ⅓ with Mono Q column buffer, fraction 5 was diluted ⅓ and fraction 6 was diluted ⅙. Fractions 5 and 6 were combined to form the "low salt pool."

FIG. **3** illustrates size-exclusion analyses of fractions from the Mono Q column in FIG. **1**, showing data obtained by a light-scattering detector at 90° and by absorbance at 276 nm, as in FIG. **2**. The fractions shown in this figure were used to form the "high salt pool", from which PEG conjugates were prepared and injected into BALB/c mice. The resultant serum activities and immunologic responses in BALB/c mice are shown in FIGS. **5** and **6**.

FIG. **4** illustrates octamer content, determined by absorbance at 276 nm and by light scattering at 90°, calculated from the data in FIGS. **2** and **3**, of unfractionated PKS uricase and of selected fractions from the preparative MonoQ column chromatography of PKS uricase (FIG. **1**).

FIG. **5** illustrates UV assays, as in FIG. **1**, of uricase activity after a 4-hour incubation at 37° C., in sera drawn 24 hours after each of six weekly injections of 6×10-kDa PEG conjugates of PKS uricase or of pools from Mono Q column fractions.

FIG. **6** illustrates ELISA analyses of IgG antibody formation against PEG conjugates of PKS uricase and against PEG conjugates of the pools of fractions from the Mono Q column shown in FIG. **1**, in sera drawn 24 hours after each of six weekly injections of female BALB/c mice with 0.2 mg of uricase protein per 20 grams of body weight. For each mouse, data from bleedings 24 hours after the first through sixth injections are shown from left to right. The assay conditions are described in Example 6. Data for the eight mice in each group were arranged in order of increasing immune response, from left to right.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

Previous studies have shown that when a significant reduction in the immunogenicity and/or antigenicity of uricase is achieved by conjugation with PEG (PEGylation), it is invariably associated with a substantial loss of uricolytic activity. The present invention includes the observation that traces of aggregates of urate oxidases larger than octamers substantially contribute to immunogenicity and the induction of accelerated clearance of PEG-uricase conjugates. This discovery is most likely applicable to proteins other than uricases, including interferons and growth factors.

The safety, convenience and cost-effectiveness of biopharmaceuticals are all adversely impacted by decreases in their potencies and the resultant need to increase the admin-

istered dose. Thus, there is a need for a safe and effective alternative means for lowering elevated levels of uric acid in body fluids, including blood and urine. The present invention provides a method for producing uricase that excludes uricase aggregates larger than octamers for use in the synthesis of PEG-uricase. This PEG-uricase retains all or nearly all of the uricolytic activity of the unmodified enzyme. The present invention also provides purified uricase substantially free of aggregates larger than octamers. The term "substantially free" indicates that the purified uricase comprises no more than about 2%, and preferably no more than about 1% of aggregates larger than octamers.

The present invention provides a method for purifying uricase such that aggregates larger then octamers are excluded from the purified preparation. Because these larger aggregates are highly immunogenic, their presence in the purified uricase preparation is undesirable. The method involves monitoring column fractions by light scattering rather than or in addition to ultraviolet absorbance at 280 nm, because the aggregates may be too dilute to be detected by ultraviolet absorbance. The purified uricase is then conjugated to water-soluble polymers, preferably poly(ethylene glycols) or poly(ethylene oxides) as described in copending U.S. application Ser. No. 09/370,084, the entire contents of which are incorporated herein by reference.

The removal of aggregated uricase from a preparation consisting predominantly of tetrameric uricase can be accomplished by any of the methods know to those skilled in the art, including size-exclusion chromatography, ion-exchange chromatography, ultrafiltration through a microporous membrane and centrifugation, including ultracentrifugation. The separation method may include separation and analysis of fractions and the rejection or exclusion of those fractions containing excessive quantities of large aggregates. The resultant uricase preparation is better suited for the synthesis of substantially non-immunogenic conjugates of uricase than is the unfractionated uricase. For chronic administration, it is important that PEG conjugates of proteins, e.g. PEG-uricase, have low immunogenicity and do not provoke progressively more rapid clearance from the bloodstream after repeated doses.

The invention also provides pharmaceutical compositions of the polymer-uricase conjugates. These conjugates are substantially non-immunogenic and retain at least 75%, preferably 85%, and more preferably 95% or more of the uricolytic activity of the unmodified enzyme. Uricases suitable for conjugation to water-soluble polymers include naturally occurring urate oxidases isolated from bacteria, fungi and the tissues of plants and animals, both vertebrates and invertebrates, as well as recombinant forms of uricase, including mutated, hybrid, and/or truncated enzymatically active variants of uricase. Water-soluble polymers suitable for use in the present invention include linear and branched poly(ethylene glycols) or poly(ethylene oxides), all commonly known as PEGs. Examples of branched PEG are the subject of U.S. Pat. No. 5,643,575. One preferred example of linear PEG is monomethoxyPEG, of the general structure $CH_3O—(CH_2CH_2O)_nH$, where n varies from about 100 to about 2,300

One embodiment of the present invention is a conjugate of urate oxidase (uricase) that retains at least about 75% of the uricolytic activity of unconjugated uricase and has substantially reduced immunogenicity. The uricase of this aspect of the invention may be recombinant. Whether recombinant or not, the uricase may be of mammalian origin. In one aspect of this embodiment, the uricase may be porcine, bovine or ovine liver uricase. In another aspect of this embodiment, the uricase may be chimeric. The chimeric uricase may contain portions of porcine liver and/or baboon liver uricase. For example, the chimeric uricase may be porcine uricase containing the mutations R291K and T301S (PKS uricase). Alternatively, the uricase may be baboon liver uricase in which tyrosine 97 has been replaced by histidine, whereby the specific activity of the uricase may be increased by at least about 60%. The uricase of the invention, whatever the origin, may also be in a form that is truncated, either at the amino terminal, or at the carboxyl terminal, or at both terminals. Likewise, the uricase may be fungal or microbial uricase. In one aspect of this embodiment, the fungal or microbial uricase may be a naturally occurring or recombinant form of uricase from *Aspergillus flavus, Arthrobacter globiformis*, Bacillus sp. or *Candida utilis*. Alternatively, the uricase may be an invertebrate uricase, such as, for example, a naturally occurring or recombinant form of uricase from *Drosophila melanogaster* or *Drosophila pseudoobscura*. The uricase of the invention may also be a plant uricase, for example, a naturally occurring or recombinant form of uricase from soybean root nodule (*Glycine max*). The PEG may have an average molecular weight between about 5 kDa and 100 kDa; preferably the PEG may have an average molecular weight between about 8 kDa and 60 kDa; more preferably, the PEG may have an average molecular weight between about 10 kDa and about 40 kDa, such as, for example, 10 to 20 kDa. The average number of covalently coupled strands of PEG may be 2 to 12 strands per uricase subunit; preferably, the average number of covalently coupled strands may be 6 to 10 per subunit; more preferably, the average number of strands of PEG may be 7 to 9 per subunit. In one aspect of this embodiment, the uricase may be tetrameric. The strands of PEG may be covalently linked to uricase via urethane (carbamate) linkages, secondary amine linkages, and/or amide linkages. When the uricase is a recombinant form of any of the uricases mentioned herein, the recombinant form may have substantially the sequence of the naturally occurring form.

One preferred mammalian uricase is recombinant pig-baboon chimeric uricase, composed of portions of the sequences of pig liver and baboon liver uricase, both of which were first determined by Wu, et al., (1989). One example of such a chimeric uricase contains the first 288 amino acids from the porcine sequence (SEQ ID NO: 1) and the last 16 amino acids from the baboon sequence (SEQ ID NO: 2). Since the latter sequence differs from the porcine sequence at only two positions, having a lysine (K) in place of arginine at residue 291 and a serine (S) in place of threonine at residue 301, this mutant is referred to as pig-K-S or PKS uricase (SEQ ID NO: 3). PKS uricase has one more lysine residue and, hence, one more potential site of PEGylation than either the porcine or baboon sequence.

The cDNAs for various mammalian uricases, including PKS uricase, were subcloned and the optimal conditions were determined for expression in *E. coli*, using standard methods. See Erlich, H A, (Ed.) (1989) *PCR Technology. Principles and Applications for DNA Amplification.* New York: Stockton Press; Sambrook, J, et al., (1989) *Molecular Cloning. A Laboratory Manual, Second Edition.* Cold Spring Harbor, NY: Cold Spring Harbor Laboratory Press. The recombinant uricases were extracted, purified and their stability and activity were assessed using a modification of standard assays. See Fridovich, I, (1965) *J Biol Chem* 240:2491–2494; Nishimura, et al., (1979), and Examples 1 and 5.

In one embodiment of the invention, uricase may be conjugated via a biologically stable, nontoxic, covalent

linkage to a relatively small number of strands of PEG. Such linkages may include urethane (carbamate) linkages, secondary amine linkages, and amide linkages. Various activated PEGs suitable for such conjugation are available commercially from Shearwater Polymers, Huntsville, AL.

For example, urethane linkages to uricase may be formed by incubating uricase in the presence of the succinimidyl carbonate (SC) or p-nitrophenyl carbonate (NPC) derivative of PEG. SC-PEG may be synthesized using the procedure described in U.S. Pat. No. 5,612,460, which is hereby incorporated by reference. NPC-PEG may be synthesized by reacting PEG with p-nitrophenyl chloroformate according to methods described in Veronese, FM, et al., (1985) *Appl Biochem Biotechnol* 11:141–152, and in U.S. Pat. No. 5,286,637, which is hereby incorporated by reference. The methods described in the '637 patent are adapted to PEGs of higher molecular weight by adjusting the concentrations of the reactants to maintain similar stoichiometry. An alternative method of synthesis of NPC-PEG is described by B üttner, W, et al., East German Patent Specification DD 279 486 A1.

Amide linkages to uricase may be obtained using an N-hydroxysuccinimide ester of a carboxylic acid derivative of PEG (Shearwater Polymers). Secondary amine linkages may be formed using 2,2,2-trifluoroethanesulfonyl PEG (tresyl PEG; Shearwater Polymers) or by reductive alkylation using PEG aldehyde (Shearvater Polymers) and sodium cyanoborohydride.

In conjugates containing PEG with a molecular weight of 10 kDa, the maximum number of strands of PEG that were coupled per subunit, while retaining at least 75% of the uricolytic activity of the unmodified enzyme, was about 12 strands for mammalian uricases (e.g. PKS uricase, a mutein of porcine uricase; see assay conditions in Example 5). The latter extent of PEGylation corresponds to about 40% of the total amino groups. In one embodiment of the invention, the average number of strands of PEG coupled per uricase subunit is between about 2 and 12. In a preferred embodiment, the average number of strands of PEG coupled per uricase subunit is between about 6 and 10. In a more preferred embodiment, the average number of covalently linked strands of PEG per uricase subunit is between about 7 and 9. In another embodiment, the molecular weight of PEG used for the coupling reaction is between about 5 kDa and 30 kDa, preferably between about 10 kDa and 20 kDa.

There are several factors that may affect the choice of the optimal molecular weight and number of strands of PEG for coupling to a given form of uricase. In general, the reduction or elimination of immunogenicity without substantial loss of uricolytic activity may require the coupling of relatively more strands of PEG of lower molecular weight, compared to relatively fewer strands of PEG of higher molecular weight. Likewise, each different form of uricase may have a different optimum with respect to both the size and number of strands. The optimal number of strands of PEG and PEG molecular weight can be readily determined using the methods described herein.

When PEG conjugates of mammalian uricase were prepared from the purified tetrameric and octameric forms of the enzyme (containing four or eight subunits of approximately 35 kDa), they displayed profoundly reduced immunogenicity in mice, in contrast to the moderate immunogenicity of PEG conjugates of uricase preparations containing large aggregates (see FIG. 6) and the very high immunogenicity of the unmodified enzyme.

Purified preparations of naturally occurring and recombinant uricases usually contain a mixture of very large aggregates of the enzyme, in addition to the tetrameric (140-kDa) and the octameric (280-kDa) forms. The percentage of each uricase preparation that is in either the tetrameric or octameric form generally varies from about 20% to 95% (see FIGS. 2–4). Despite evidence that unPEGylated aggregates of several other proteins are highly immunogenic (see, e.g., Moore, W V, et al., (1980) *J Clin Endocrinol Metab* 51:691–697), previous studies of PEG-uricase do not describe any efforts to limit the content of aggregates, suggesting that the potential immunogenicity of the PEG-modified aggregates was not considered. On the basis of the observations of the present inventors, it appears likely that such aggregates were present in the enzyme preparations used for previous syntheses of PEG-uricase. Their presence may have rendered the task of preparing non-immunogenic conjugates more difficult. It also appears that the large losses of uricolytic activity observed in previous efforts to PEGylate uricase were related to the large number of strands of low molecular weight PEG that were coupled. On the other hand, the methods of uricase purification and PEGylation described herein permit the covalent attachment of as many as 12 strands of PEG per subunit while retaining more than 75% of the uricolytic activity, at least for certain uricases, e.g., PKS uricase (a mutein of porcine uricase) and the enzyme from thermophilic Bacillus sp.

In another preferred embodiment, substantially all large aggregates of the enzyme may be removed by ion-exchange chromatography (FIGS. 1–3) or size-exclusion chromatography at a pH between about 9 and 10.5, preferably 10.2, prior to conjugation of the resulting substantially aggregate-free preparation of uricase to PEG. The molecular weight of the uricase in each fraction from the preparative column may be monitored by any size-dependent analytical technique, including, for example, HPLC, conventional size-exclusion chromatography, centrifugation, light scattering, capillary electrophoresis or gel electrophoresis in a non-denaturing buffer. For aggregate-free uricase isolated using size-exclusion chromatography, fractions containing only the 140-kDa and 280-kDa forms of the enzyme may be pooled and used for conjugation to PEG. For tetrameric plus octameric uricase isolated using ion-exchange chromatography, fractions from the ion-exchange column may be analyzed with respect to size to determine which fractions contain substantial amounts of the tetrameric and octameric forms without the large aggregates detected by light scattering. In the purified product, the undesirable large aggregates may thus constitute as little as about 1%, or less, of the total uricase.

The results presented herein indicate that, even when extensively PEGylated, forms of PKS uricase larger than the octamer provoke accelerated clearance (FIG. 5) and are somewhat immunogenic in mice (FIG. 6). In contrast, conjugates prepared from uricase that is essentially free of large aggregates (detectable by light scattering) could be reinjected at least six times at one-week intervals with much less evidence of accelerated clearance rates (FIG. 5) and without the detectable formation of antibodies, as measured by a sensitive enzyme-linked immunoassay (FIG. 6). The use of highly purified tetrameric or octameric uricase further distinguishes the improved conjugates of the present invention from the PEG-uricase preparations described previously. In contrast, the presence of a significant content of large aggregates in the uricase preparations used by some previous investigators may have led them to couple large numbers of strands of PEG in efforts to suppress the immunogenicity. Consequently, the enzymatic activity of the resultant conjugates was decreased substantially.

The PEG-uricase conjugates of the present invention are useful for lowering the levels of uric acid in the body fluids and tissues of mammals, preferably humans, and can thus be used for treatment of elevated uric acid levels associated with conditions including gout, tophi, renal insufficiency, organ transplantation and malignant disease. PEG-uricase conjugates may be injected into a mammal having excessive uric acid levels by any of a number of routes, including intravenous, subcutaneous, intradermal, intramuscular and intraperitoneal routes. Alternatively, they may be aerosolized and inhaled. See Patton, JS, (1996) *Adv Drug Delivery Rev* 19:3–36 and U.S. Pat. No. 5,458,135. The effective dose of PEG-uricase of the present invention will depend on the level of uric acid and the size of the individual. In one embodiment of this aspect of the invention, PEG-uricase is administered in a pharmaceutically acceptable excipient or diluent in an amount ranging from about 10 μg to about 1 g. In a preferred embodiment, the amount administered is between about 100 μg and 500 mg. More preferably, the conjugated uricase is administered in an amount between 1 mg and 100 mg, such as, for example, 5 mg, 20 mg or 50 mg. Masses given for dosage amounts of the embodiments refer to the amount of protein in the conjugate.

Pharmaceutical formulations containing PEG-uricase can be prepared by conventional techniques, e.g., as described in Gennaro, AR (Ed.) (1990) *Remington's Pharmaceutical Sciences*, 18th Edition, Easton, Pa.: Mack Publishing Co. Suitable excipients for the preparation of injectable solutions include, for example, phosphate buffered saline, lactated Ringer's solution, water, polyols and glycerol. Pharmaceutical compositions for parenteral injection comprise pharmaceutically acceptable sterile aqueous or non-aqueous liquids, dispersions, suspensions, or emulsions as well as sterile powders for reconstitution into sterile injectable solutions or dispersions just prior to use. These formulations may contain additional components, such as, for example, preservatives, solubilizers, stabilizers, wetting agents, emulsifiers, buffers, antioxidants and diluents.

PEG-uricase may also be provided as controlled-release compositions for implantation into an individual to continually control elevated uric acid levels in body fluids. For example, polylactic acid, polyglycolic acid, regenerated collagen, poly-L-lysine, sodium alginate, gellan gum, chitosan, agarose, multilamellar liposomes and many other conventional depot formulations comprise bioerodible or biodegradable materials that can be formulated with biologically active compositions. These materials, when implanted or injected, gradually break down and release the active material to the surrounding tissue. For example, one method of encapsulating PEG-uricase comprises the method disclosed in U.S. Pat. No. 5,653,974, which is hereby incorporated by reference. The use of bioerodible, biodegradable and other depot formulations is expressly contemplated in the present invention. The use of infusion pumps and matrix entrapment systems for delivery of PEG-uricase is also within the scope of the present invention. PEG-uricase may also advantageously be enclosed in micelles or liposomes. Liposome encapsulation technology is well known in the art. See, e.g., Lasic, D, et al., (Eds.) (1995) *Stealth Liposomes*. Boca Raton, Fla.: CRC Press.

The PEG-uricase pharmaceutical compositions of the invention will decrease the need for hemodialysis in patients at high risk of urate-induced renal failure, e.g., organ transplant recipients (see Venkataseshan, VS, et al., (1990) *Nephron* 56:317–321) and patients with some malignant diseases. In patients with large accumulations of crystalline urate (tophi), such pharmaceutical compositions will improve the quality of life more rapidly than currently available treatments.

The following examples, which are not to be construed as limiting the invention in any way, illustrate the various aspects disclosed above. These examples describe PEG-uricases prepared by coupling activated PEG (e.g., the p-nitrophenyl carbonate derivative) to a mutein of porcine uricases. These examples provide guidance to one of ordinary skill in the art for producing substantially non-immunogenic conjugates of uricase that retain at least about 75% of the uricolytic activity of the unmodified enzyme and are well suited for chronic administration.

EXAMPLE 1

Preparative Ion-exchange Chromatography of Uricase

Preparative ion-exchange chromatography was performed on a Fast Protein Liquid Chromatography (FPLC) apparatus (Amersham Pharmacia, Piscataway, N.J.). The Mono Q column (1×10 cm, Amersham Pharmacia) was eluted with a gradient of 50 mM sodium carbonate, pH 10.3, 0.1 M NaCl (Buffer A) to 50 mM sodium carbonate, pH 10.3, 0.6 M NaCl (Buffer B) at a flow rate of 0.5 ml/min, except that the sample was loaded at a lower flow-rate. This technique was used to fractionate 25 mL of a solution of PKS uricase (pH 10.3). PKS uricase was obtained from Bio-Technology General Limited (Rehovot, Israel). The latter is recombinant porcine uricase in which one residue of lysine (K) and one residue of serine (S) have replaced one residue of arginine and one residue of threonine, respectively, in the parental porcine sequence (Lee et al. (1988) Science 239:1288–1291; Wu et al. (1989) *Proc. Natl. Acad. Sci. U. S. A.* 86::9412–9416). After the sample was loaded, the column was washed with 100 mL of Buffer A. The peak of uricase began to elute at the end of a 31-mL linear gradient of 0 to 26% Buffer B. Most of the uricase was eluted isocratically by 7mL of buffer containing 26% Buffer B. The remainder of the recovered uricase was eluted by a linear 89-mL gradient of 26% to 100% buffer B. Fractions of 4 mL or 6 mL were collected. Aliquots of Fractions #4–11 were assayed for uricase, total protein and NaCl concentration (FIG. 1) and were analyzed by size-exclusion high performance liquid chromatography (HPLC) as described in Example 2 (FIGS. 2 and 3). The remaining portions of Fractions #5–10 were coupled to PEG, as described in Example 3. Based on the results of the analyses in Example 2, the PEG conjugates of Fractions #5 and 6 were combined as the "Low-Salt Pool" and the PEG conjugates of Fractions #7–10 were combined as the "High-Salt Pool," as indicated in FIG. 1.

EXAMPLE 2

Size-exclusion Chromatography of Uricase Monitored by Light Scattering and Ultraviolet Absorbance

Size-exclusion HPLC was performed at room temperature on a Superdex 200 column (1×30 cm, Amersham Pharmacia Biotech) on unfractionated PKS uricase and on selected fractions from the preparative Mono Q chromatography of PKS uricase of Example 1. The eluate from the absorbance monitor (UV 2000) of the Thermo Separations HPLC (Sunnyvale, Calif.) was analyzed by light scattering at 90° to the incident light, using a MiniDawn detector from Wyatt Technologies (Santa Barbara, Calif.).

The results shown in FIGS. 2–4 illustrate the resolution among the tetramer, octamer and larger aggregates of the uricase subunit and the different proportions of the signals detected from these forms of uricase in the various samples. Unlike the absorbance signal, which is directly proportional to the concentration, the light scattering signal is proportional to the product of the concentration times the size of the light scattering unit. The resultant sensitivity of the light scattering detector to very small amounts of highly aggregated uricase revealed the presence of the largest aggregates, which are eluted at or near the void volume (approximately 7 mL).

EXAMPLE 3

Synthesis of PEG-uricase Conjugates

Unfractionated PKS uricase (from Bio-Technology General Limited) and the uricase in fractions from the Mono Q column of Example 1 were coupled to 10-kDa PEG using the p-nitrophenyl carbonate derivative of PEG (NPC-PEG) obtained from Shearwater Polymers (Huntsville, Ala.). The preparation of NPC-PEG from PEG using phenylchloroformates has been described in several reports (e.g. Veronese, FM, et al., (1985) *Appl Biochem Biotechnol* 11:141–152; Kito, M, et al., (1996) *J Clin Biochem Nutr* 21:101–111) and NPC-PEG has been used for the synthesis of PEG-protein conjugates by previous investigators including the present inventors (e.g. Veronese et al., supra; Sherman M R, et al., in J M Harris, et al., (Eds.) *Poly(ethylene glycol) Chemistry and Biological Applications ACS Symposium Series* 680 (pp. 155–1706 Washington, D.C.: American Chemical Society). The number of strands of 10-kDa PEG coupled to each subunit of uricase was determined to be six by the method described by Kunitani, M, et al., (1991) *J Chromatogr* 588:125–137.

EXAMPLE 4

In Vivo Serum Persistence and immunogenicity of Uricase and PEG-uricase

PEG conjugates of recombinant mammalian uricases, prepared according to the method of Example 3, were adjusted to 1 mg protein/mL in phosphate-buffered saline (PBS), pH 7.4, for injection. Samples were frozen and stored until analyzed or injected. Samples were warmed to 37° C. for up to 1 hour prior to injection into groups of eight BALB/c female mice. The groups of mice had mean weights in the range of 18–22 g at the start of the studies.

The weights of all mice were monitored and evidence of adverse reactions to the injections or other evidence of ill health was recorded. Twenty-four hours after each of six weekly injections, the animals were anesthetized with ketamine and 100–200 μL of blood was obtained retro-orbitally, except at sacrifice (exsanguination), when a larger volume was collected. Serum was prepared from blood that had clotted for between 4 and 32 hours at 2–8° C. Sera were stored at −20° C. Sera were analyzed for uricolytic activity as described in Example 5 and analyzed for antibodies against uricases as described in Example 6.

EXAMPLE 5

Uricolytic Activity Assays of PEG-uricase in Sera from Mice Injected with PEG-uricase

An activity assay based on ultraviolet light absorbance (UV assay) was performed with 100 μM uric acid as the substrate in 200 mM sodium borate, pH 9.2, in a microplate adaptation of the method of I. Fridovich (*J Biol Chem.* (1965) 240:2491–2494). The decrease in absorbance at 292 nm was monitored for 15 minutes at room temperature in a 96-well plate with a UV-transparent bottom (Costar, Corning, N.Y.), using a SpectraMAX 250 microplate reader from Molecular Devices (Sunnyvale, Calif.). The data were analyzed by finding the maximum slope (in milli-absorbance units per minute) of absorbance measurements made during the interval while between 10 and 40% of the substrate was oxidized. Results obtained with this assay are illustrated in FIGS. 1 and 5.

The mean half-life in sera of mice injected for the first time with PKS uricase coupled to six strands of 10-kDa PEG per subunit (6×10-kDa PEG PKS) was 29±4 hours, based on data from sera obtained 24 and 72 hours after the injection.

In separate experiments, it was established that the detectable uricolytic activity in the sera of mice injected with PEG-uricase declines during storage at −20° C. and that maximal recovery of this activity is obtained by a 4-hour incubation at 37° prior to assay. FIG. 5 shows that the recovery of uricolytic activity after repeated weekly injections of 6×10-kDa PEG PKS uricase was greatest when the enzyme was purified by Mono Q column chromatography, as in Example 1, prior to PEGylation according to the method of Example 3. Recovery was highest after the injection of conjugates prepared from the high-salt eluate pool of Example 1 (see FIG. 1), which has the smallest content of the very large aggregates (see the light scattering profiles of Fractions 7–10 in FIG. 3). Intermediate recovery was obtained with conjugates prepared from the low-salt eluate pool from the Mono Q column of Example 1, and the poorest recovery was obtained with conjugates made from unfractionated PKS uricase, which has the highest content of very large aggregates (see FIG. 2). The same order of relative activities recovered in sera after repeated injections (high salt pool>low salt pool>unfractionated uricase) was observed regardless of whether the UV assay described above or a colorimetric assay adapted from P. Fossati et al. (*J. Clin Chem* (1980) 26:227–231), was used and regardless of whether the sera were incubated at 37° C. before they were assayed.

EXAMPLE 6

Enzyme-linked Immunosorbent Assay (ELISA) of Sera from Mice Injected with PEG-uricase

Non-competitive ELISA analyses were performed with porcine uricase bound to 96-well Immulon 2 plates (Dynex Technologies, from VWR Scientific, San Francisco, CA). The primary antisera were from mice injected with uricase or 6×10-kDa PEG conjugates prepared according to the method of Example 3. The secondary antibody was goat anti-mouse IgG coupled to horseradish peroxidase (Calbiochem-Novabiochem #401 253, La Jolla, Calif.) and the substrate was o-phenylenediamine dihydrochloride (Sigma P-9187, St. Louis, Mo.), as described by B. Porstmann et al. (*J Clin. Chem. Clin. Biochem.* (1981) 19:435–440).

FIG. 6 illustrates the results of the non-competitive ELISA analyses. The results demonstrate that the 6×10-kDa PEG PKS uricase synthesized according to the method of Example 3 from the high-salt eluate from the Mono Q column of Example 1 (shown in FIG. 1) did not produce detectable immune responses in any of the eight mice that

received weekly injections for six weeks. A few mice injected with conjugates prepared from unfractionated PKS uricase according to the method of Example 3 showed low but detectable immune responses. The highest incidence of immune responses was in mice injected with conjugates prepared according to the method of Example 3 from the low-salt eluate pool from the Mono Q column of Example 1.

Without the benefit of the light scattering detector for the size-exclusion HPLC analyses, as described in Example 2, it would not have been apparent that the presence of the largest aggregates, not of the octameric form of uricase, is associated with progressively decreased recovery of PEG-uricase conjugates after repeated injections, as observed in Example 5 (FIG. 5) and with an increase in immunogenicity in BALB/c mice, as observed in Example 6 (FIG. 6). These results have important implications for the specifications of the uricase used as a starting material for the production of PEG-uricase for clinical use.

Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it is readily apparent to those of ordinary skill in the art in light of the teachings of this invention that certain changes and modifications may be made thereto without departing from the spirit and scope of that which is described and claimed.

SEQUENCE LISTING

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<213> ORGANISM: Sus scrofa

<400> SEQUENCE: 1

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Arg Asp Gly Lys Tyr His Ser Ile Lys Glu Val Ala Thr Ser Val Gln
        35                  40                  45

Leu Thr Leu Ser Ser Lys Lys Asp Tyr Leu His Gly Asp Asn Ser Asp
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Val Ile Pro Thr Asp Thr Ile Lys Asn Thr Val Asn Val Leu Ala Lys
65                  70                  75                  80

Phe Lys Gly Ile Lys Ser Ile Glu Thr Phe Ala Val Thr Ile Cys Glu
                85                  90                  95

His Phe Leu Ser Ser Phe Lys His Val Ile Arg Ala Gln Val Tyr Val
            100                 105                 110

Glu Glu Val Pro Trp Lys Arg Phe Glu Lys Asn Gly Val Lys His Val
        115                 120                 125

His Ala Phe Ile Tyr Thr Pro Thr Gly Thr His Phe Cys Glu Val Glu
    130                 135                 140

Gln Ile Arg Asn Gly Pro Pro Val Ile His Ser Gly Ile Lys Asp Leu
145                 150                 155                 160

Lys Val Leu Lys Thr Thr Gln Ser Gly Phe Glu Gly Phe Ile Lys Asp
                165                 170                 175

Gln Phe Thr Thr Leu Pro Glu Val Lys Asp Arg Cys Phe Ala Thr Gln
            180                 185                 190

Val Tyr Cys Lys Trp Arg Tyr His Gln Gly Arg Asp Val Asp Phe Glu
        195                 200                 205

Ala Thr Trp Asp Thr Val Arg Ser Ile Val Leu Gln Lys Phe Ala Gly
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Pro Tyr Asp Lys Gly Glu Tyr Ser Pro Ser Val Gln Lys Thr Leu Tyr
225                 230                 235                 240

Asp Ile Gln Val Leu Thr Leu Gly Gln Val Pro Glu Ile Glu Asp Met
                245                 250                 255

Glu Ile Ser Leu Pro Asn Ile His Tyr Leu Asn Ile Asp Met Ser Lys
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-continued

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            260                 265                 270

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Arg Asp Gly Lys Tyr His Ser Ile Lys Glu Val Ala Thr Ser Val Gln
        35                  40                  45

Leu Thr Leu Ser Ser Lys Lys Asp Tyr Leu His Gly Asp Asn Ser Asp
    50                  55                  60

Ile Ile Pro Thr Asp Thr Ile Lys Asn Thr Val His Val Leu Ala Lys
65                  70                  75                  80

Phe Lys Gly Ile Lys Ser Ile Glu Ala Phe Gly Val Asn Ile Cys Glu
                85                  90                  95

Tyr Phe Leu Ser Ser Phe Asn His Val Ile Arg Ala Gln Val Tyr Val
            100                 105                 110

Glu Glu Ile Pro Trp Lys Arg Leu Glu Lys Asn Gly Val Lys His Val
        115                 120                 125

His Ala Phe Ile His Thr Pro Thr Gly Thr His Phe Cys Glu Val Glu
    130                 135                 140

Gln Leu Arg Ser Gly Pro Pro Val Ile His Ser Gly Ile Lys Asp Leu
145                 150                 155                 160

Lys Val Leu Lys Thr Thr Gln Ser Gly Phe Glu Gly Phe Ile Lys Asp
                165                 170                 175

Gln Phe Thr Thr Lys Pro Glu Val Lys Asp Arg Cys Phe Ala Thr Gln
            180                 185                 190

Val Tyr Cys Lys Trp Arg Tyr His Gln Cys Arg Asp Val Asp Phe Glu
        195                 200                 205

Ala Thr Trp Gly Thr Ile Arg Asp Leu Val Leu Glu Lys Phe Ala Gly
    210                 215                 220

Pro Tyr Asp Lys Gly Glu Tyr Ser Pro Ser Val Gln Lys Thr Leu Tyr
225                 230                 235                 240

Asp Ile Gln Val Leu Ser Leu Ser Arg Val Pro Glu Ile Glu Asp Met
                245                 250                 255

Glu Ile Ser Leu Pro Asn Ile His Tyr Phe Asn Ile Asp Met Ser Lys
            260                 265                 270

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            20                  25                  30

Arg Asp Gly Lys Tyr His Ser Ile Lys Glu Val Ala Thr Ser Val Gln
        35                  40                  45

Leu Thr Leu Ser Ser Lys Lys Asp Tyr Leu His Gly Asp Asn Ser Asp
    50                  55                  60

Val Ile Pro Thr Asp Thr Ile Lys Asn Thr Val Asn Val Leu Ala Lys
65                  70                  75                  80

Phe Lys Gly Ile Lys Ser Ile Glu Thr Phe Ala Val Thr Ile Cys Glu
                85                  90                  95

His Phe Leu Ser Ser Phe Lys His Val Ile Arg Ala Gln Val Tyr Val
            100                 105                 110

Glu Glu Val Pro Trp Lys Arg Phe Glu Lys Asn Gly Val Lys His Val
        115                 120                 125

His Ala Phe Ile Tyr Thr Pro Thr Gly Thr His Phe Cys Glu Val Glu
    130                 135                 140

Gln Ile Arg Asn Gly Pro Pro Val Ile His Ser Gly Ile Lys Asp Leu
145                 150                 155                 160

Lys Val Leu Lys Thr Thr Gln Ser Gly Phe Glu Gly Phe Ile Lys Asp
                165                 170                 175

Gln Phe Thr Thr Leu Pro Glu Val Lys Asp Arg Cys Phe Ala Thr Gln
            180                 185                 190

Val Tyr Cys Lys Trp Arg Tyr His Gln Gly Arg Asp Val Asp Phe Glu
        195                 200                 205

Ala Thr Trp Asp Thr Val Arg Ser Ile Val Leu Gln Lys Phe Ala Gly
    210                 215                 220

Pro Tyr Asp Lys Gly Glu Tyr Ser Pro Ser Val Gln Lys Thr Leu Tyr
225                 230                 235                 240

Asp Ile Gln Val Leu Thr Leu Gly Gln Val Pro Glu Ile Glu Asp Met
                245                 250                 255

Glu Ile Ser Leu Pro Asn Ile His Tyr Leu Asn Ile Asp Met Ser Lys
            260                 265                 270

Met Gly Leu Ile Asn Lys Glu Glu Val Leu Leu Pro Leu Asp Asn Pro
        275                 280                 285

Tyr Gly Lys Ile Thr Gly Thr Val Lys Arg Lys Leu Ser Ser Arg Leu
    290                 295                 300
```

What is claimed is:

1. Purified urate oxidase (uricase) that contains no more than about 2% of aggregates larger than octamers, wherein greater than about 20% of said uricase is in the tetrameric or octameric form.

2. The uricase of claim 1, wherein the uricase is mammalian uricase.

3. The uricase of claim 2, wherein the uricase is porcine liver, bovine liver or ovine liver uricase.

4. The uricase of claim 1, wherein the uricase is recombinant.

5. The uricase of claim 4, wherein the uricase has the sequence of porcine, bovine, ovine or baboon liver uricase.

6. The uricase of claim 4, wherein the uricase is chimeric.

7. The uricase of claim 6, wherein the chimeric uricase contains portions of porcine liver and baboon liver uricase.

8. The uricase of claim 7, wherein the chimeric uricase is porcine uricase in which arginine residue 291 of SEQ ID NO:2 has been replaced by lysine (R291 K) and threonine residue 301 of SEQ ID NO:2 has been replaced by serine (T301 S) (PKS uricase).

9. The uricase of claim 4, wherein the uricase has the sequence as set forth in SEQ ID NO:2, wherein tyrosine 97 has been replaced by histidine.

10. The uricase of claim 1, wherein the uricase is a fungal or microbial uricase.

11. The uricase of claim 10, wherein the fungal or microbial uricase is isolated from *Aspergillus flavus, Arthrobacter globiformis*, Bacillus sp. or *Candida utilis*, or is a recombinant enzyme having the sequence of one of said uricases.

12. The uricase of claim 1, wherein the uricase is an invertebrate uricase.

13. The uricase of claim 12, wherein the invertebrate uricase is isolated from *Drosophila melanogaster* or *Drosophila pseudoobscura*, or is a recombinant enzyme having the sequence of one of said uricases.

14. The uricase of claim 1, wherein the uricase is a plant uricase.

15. The uricase of claim 14, wherein the plant uricase is isolated from root nodules of *Glycine max* or is a recombinant enzyme having the sequence of said uricase.

16. A uricase conjugate comprising the uricase of claim 1 conjugated to poly(ethylene glycol) or poly(ethylene oxide).

17. The uricase conjugate of claim 16, wherein said poly(ethylene glycol) is monomethoxy poly(ethylene glycol).

18. The uricase conjugate of claim 16, wherein said uricase is conjugated to said poly(ethylene glycol) or poly (ethylene oxide) via a linkage selected from the group consisting of urethane (carbamate), secondary amine and amide.

19. The uricase conjugate of claim 16, wherein said poly(ethylene glycol) or poly(ethylene oxide) has a molecular weight between about 5 kDa and 30 kDa.

20. The uricase conjugate of claim 19, wherein said poly(ethylene glycol) or poly(ethylene oxide) has a molecular weight between about 10 kDa and 20 kDa.

21. The uricase conjugate of claim 16, wherein the average number of strands of said poly(ethylene glycol) or poly(ethylene oxide) is between about 2 and 12 per uricase subunit.

22. The uricase conjugate of claim 21, wherein the average number of strands of said poly(ethylene glycol) or poly(ethylene oxide) is between about 6 and 10 per uricase subunit.

23. The uricase conjugate of claim 22, wherein the average number of strands of said poly(ethylene glycol) or poly(ethylene oxide) is between about 7 and 9 per uricase subunit.

24. The uricase conjugate of claim 16, wherein the poly(ethylene glycol) or poly(ethylene oxide) is linear.

25. The uricase conjugate of claim 16, wherein the poly(ethylene glycol) or poly(ethylene oxide) is branched.

26. A pharmaceutical composition for lowering uric acid levels in a body fluid or tissue, comprising the conjugate of claim 16 and a pharmaceutically acceptable carrier.

27. The pharmaceutical composition of claim 26, wherein said composition is stabilized by lyophilization and dissolves upon reconstitution to provide solutions suitable for parenteral administration.

28. A purified fragment of uricase that contains no more than about 2% of aggregates larger than octamers, wherein said fragment is a recombinant uricase that has been truncated at the amino terminus, at the carboxyl terminus, or at both the amino and carboxyl termini, and wherein greater than about 20% of said truncated uricase is in the tetrameric or octameric form.

29. The purified uricase of claim 1, wherein about 98% to about 100% of said uricase is in the tetrameric or octameric form.

30. Isolated uricase prepared by a method comprising separating uricase aggregates larger than octamers from uricase tetramers and octamers and excluding such aggregates from the isolated uricase, wherein about 98% to about 100% of said uricase is in the tetrameric or octameric form.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,783,965 B1
APPLICATION NO. : 09/501730
DATED : August 31, 2004
INVENTOR(S) : Sherman et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the Title page, 1st column, please delete Item (75), "Merry R. Sherman, San Carlos, CA (US); Mark G.P. Saifer, San Carlos, CA (US); L. David Williams, Fremont, CA (US);" and insert therein -- Merry R. Sherman, San Carlos, CA (US); Mark G.P. Saifer, San Carlos, CA (US); L. David Williams, Fremont, CA (US); Michael S. Hershfield, Durham, NC (US); Susan J. Kelly, Chapel Hill, NC (US);--

and

In column 18, Line 52-57 please delete claim 8, "The uricase of claim 7, wherein the chimeric uricase is porcine uricase in which arginine residue 291 of SEQ ID NO:2 has been replaced by lysine (R291 K) and threonine residue 301 of SEQ ID NO:2 has been replaced by serine (T301 S) (PKS uricase)." and insert therein --The uricase of claim 7, wherein the chimeric uricase is porcine uricase in which arginine residue 291 of SEQ ID NO:1 has been replaced by lysine (R291 K) and threonine residue 301 of SEQ ID NO:1 has been replaced by serine (T301 S) (PKS uricase). --

Signed and Sealed this

Nineteenth Day of December, 2006

JON W. DUDAS
Director of the United States Patent and Trademark Office

Disclaimer

6,783,965 — Merry R. Sherman, San Carlos, CA (US); Mark G. P. Saifer, San Carlos, CA (US); and L. David Williams, Fremont, CA (US). AGGREGATE-FREE URATE OXIDASE FOR PREPARATION OF NON-IMMUNOGENIC POLYMER CONJUGATES. Patent dated August 31, 2004. Disclaimer filed August 05, 2008, by the assignee, Mountain View Pharmaceuticals, Inc.

The term of this patent should not extend beyond the expiration date of Patent No. 6,576,235.

(Official Gazette November 25, 2008)

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,783,965 B1
APPLICATION NO. : 09/501730
DATED : August 31, 2004
INVENTOR(S) : Sherman et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the Title page of the patent, please replace exemplary drawing FIG. 1 with corrected FIG. 1.

Also, please replace FIG. 1 and FIG. 5 with corrected replacement figures attached herein.

Signed and Sealed this

First Day of September, 2009

David J. Kappos

David J. Kappos
Director of the United States Patent and Trademark Office

(12) **United States Patent**
Sherman et al.

(10) **Patent No.: US 6,783,965 B1**
(45) **Date of Patent: *Aug. 31, 2004**

(54) **AGGREGATE-FREE URATE OXIDASE FOR PREPARATION OF NON-IMMUNOGENIC POLYMER CONJUGATES**

(75) Inventors: **Merry R. Sherman**, San Carlos, CA (US); **Mark G. P. Saifer**, San Carlos, CA (US); **L. David Williams**, Fremont, CA (US)

(73) Assignee: **Mountain View Pharmaceuticals, Inc.**, Menlo Park, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **09/501,730**

(22) Filed: **Feb. 10, 2000**

(51) **Int. Cl.**[7] **C12N 9/84**; C12N 15/00; A61K 38/44; C07K 1/00; C07H 21/04

(52) **U.S. Cl.** **435/190**; 435/191; 435/440; 424/94.4; 536/23.2; 530/350

(58) **Field of Search** 435/190, 191, 435/440, 170; 424/94.4, 94.6; 536/23.2; 530/350, 413

(56) **References Cited**

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Caliceti et al. Biopharmaceutical properties of uricase conjugated to neutral and amphiphilic polymer. Bioconjugate Chem. 10, 638–646. (1999).*

(List continued on next page.)

Primary Examiner—Ponnathapu Achutamurthy
Assistant Examiner—Yong Pak
(74) *Attorney, Agent, or Firm*—Sterne, Kessler, Goldstein & Fox P.L.L.C.

(57) **ABSTRACT**

A naturally occurring or recombinant protein, especially a mutein of porcine urate oxidase (uricase), that is essentially free of large aggregates can be rendered substantially non-immunogenic by conjugation with a sufficiently small number of strands of polymer such that the bioactivity of the protein is essentially retained in the conjugate. Such conjugates are unusually well suited for treatment of chronic conditions because they are less likely to induce the formation of antibodies and/or accelerated clearance than are similar conjugates prepared from protein preparations containing traces of large aggregates.

30 Claims, 6 Drawing Sheets

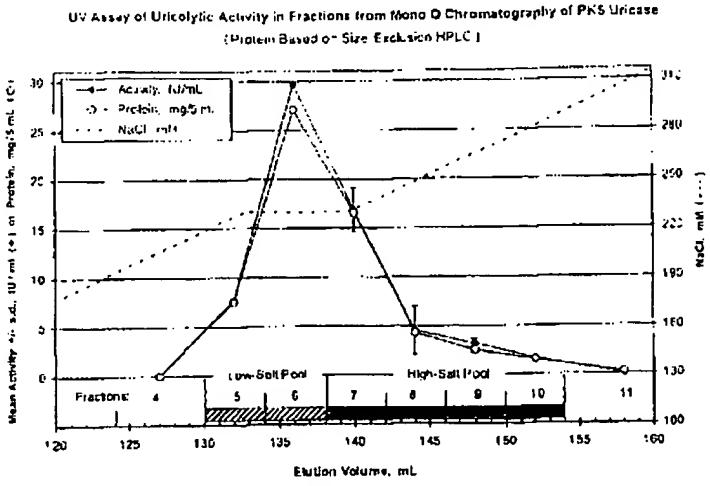


FIG. 1

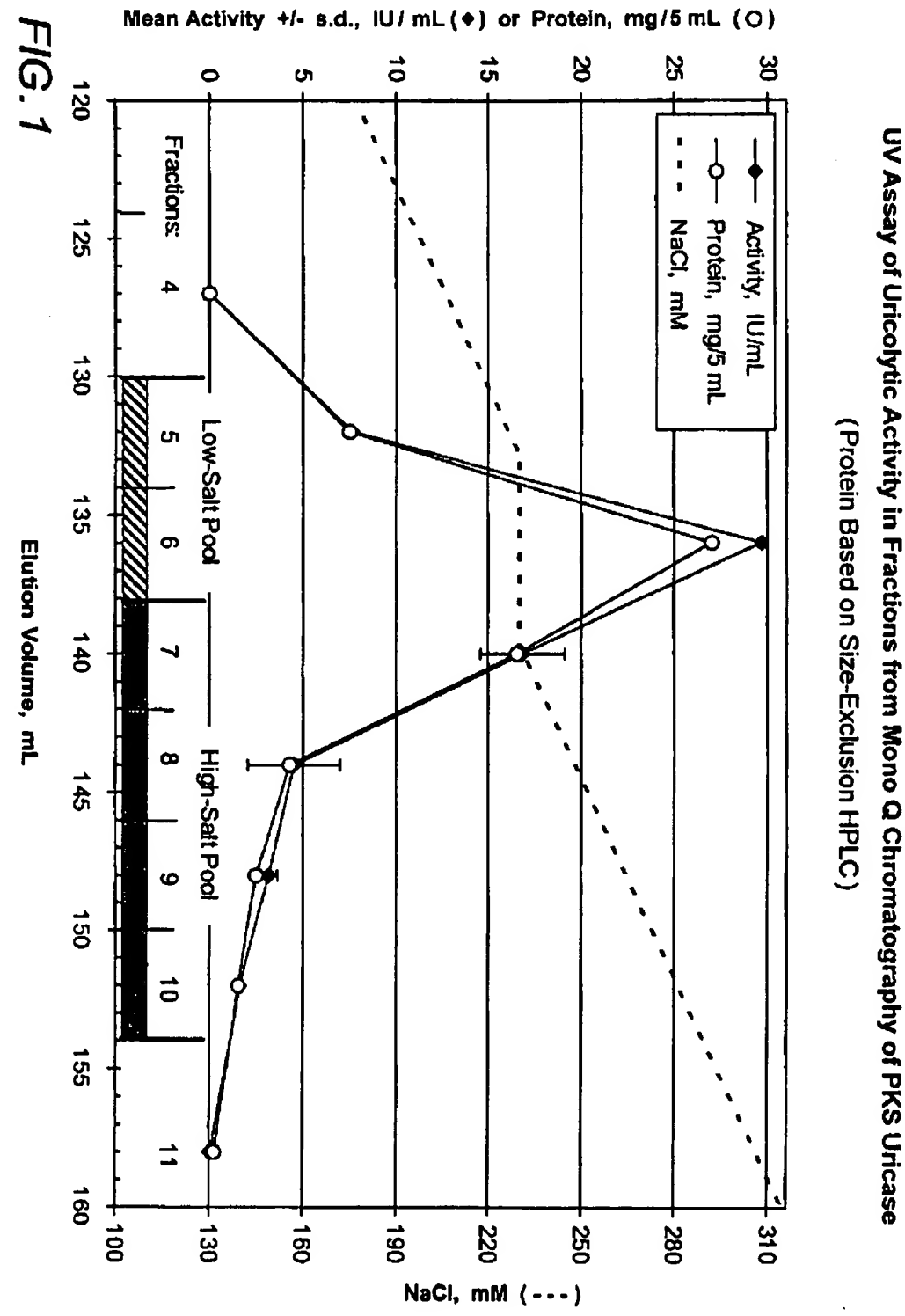
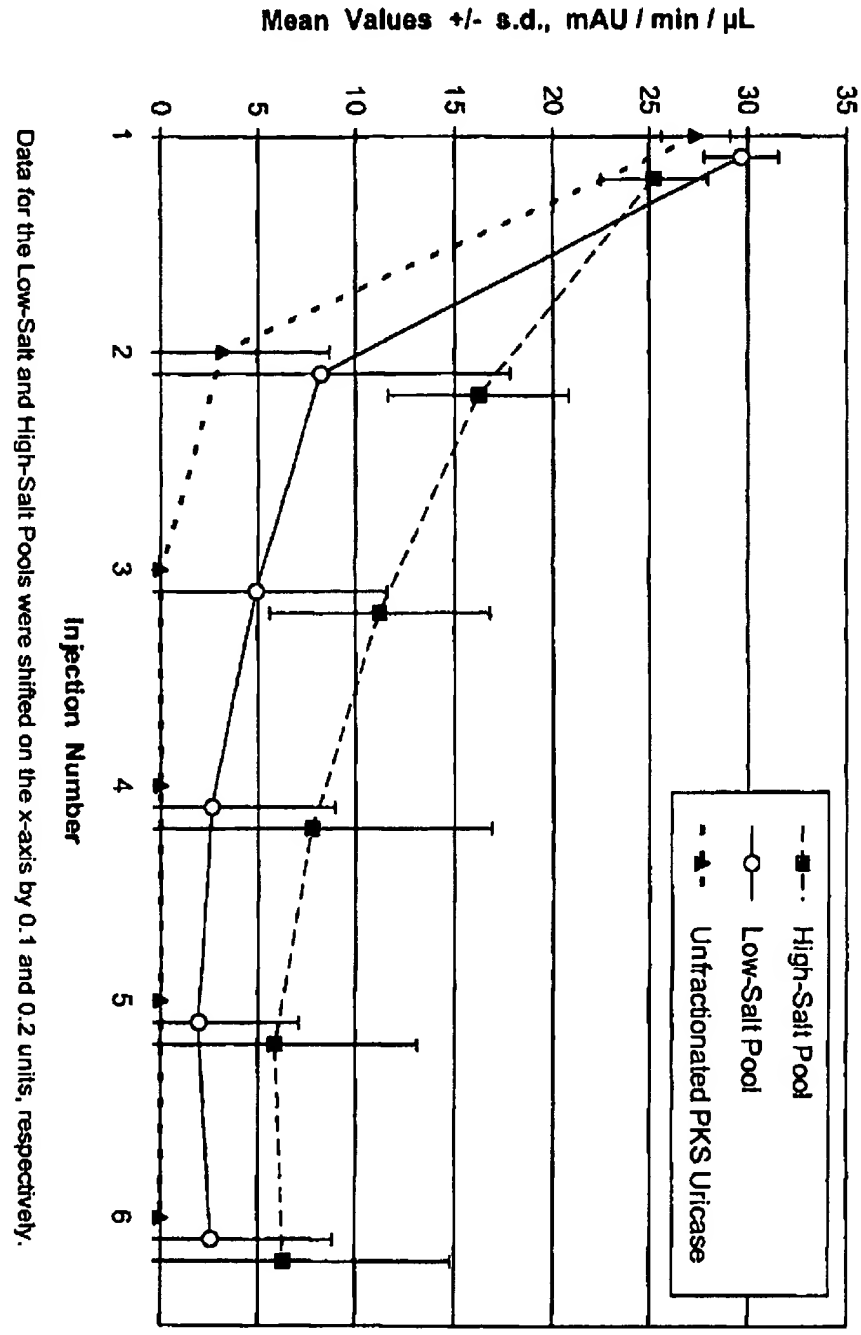

UV Assay of Uricolytic Activity in Fractions from Mono Q Chromatography of PKS Uricase
(Protein Based on Size-Exclusion HPLC)
Mean Activity +/- s.d., IU/mL (◆) or Protein, mg/5 mL (○)
Activity, IU/mL
Protein, mg/5 mL
NaCl, mM
NaCl, mM (- - -)
Elution Volume, mL
Fractions: 4 5 6 7 8 9 10 11
Low-Salt Pool
High-Salt Pool
0 5 10 15 20 25 30
100 130 160 190 220 250 280 310
120 125 130 135 140 145 150 155 160

FIG. 5

UV Uricase Assays of Sera from Mice Injected with 6 x 10-kDa PEG Conjugates of PKS Uricase or of Pools from Mono Q Column Fractions

(Mice Were Bled 24 Hours after Each Weekly Injection.)



Data for the Low-Salt and High-Salt Pools were shifted on the x-axis by 0.1 and 0.2 units, respectively.

EXHIBIT 6

PTO/SB/26 (08-03)
Approved for use through 07/31/2006. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

TERMINAL DISCLAIMER TO OBVIATE A DOUBLE PATENTING REJECTION OVER A PRIOR PATENT	Docket Number (Optional) 2057.0080000/BJD

In re Application of: SHERMAN *et al.*

Application No.: 09/501,730

Filed: February 10, 2000

For: **Aggregate-Free Urate Oxidase for Preparation of Non-Immunogenic Polymer Conjugates**

The owner*, Mountain View Pharmaceuticals, Inc., of 100 percent interest in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term defined in 35 U.S.C. 154 and 173, as presently shortened by any terminal disclaimer, of prior Patent No. 6,576,235. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the prior patent are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the owner does not disclaim the terminal part of any patent granted on the instant application that would extend to the expiration date of the full statutory term as defined in 35 U.S.C. 154 and 173 of the prior patent, as presently shortened by any terminal disclaimer, in the event that it later: expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of competent jurisdiction, is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321, has all claims canceled by a reexamination certificate, is reissued, or is in any manner terminated prior to the expiration of its full statutory term as presently shortened by any terminal disclaimer.

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

2. ☒ The undersigned is an attorney or agent of record.

Signature Dec. 4, 2003
Date

Brian J. Del Buono, Reg. No. 42,473
Typed or printed name

202-371-2600
Telephone Number

☒ Terminal disclaimer fee under 37 CFR 1.20(d) included.

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

*Statement under 37 CFR 3.73(b) is required if terminal disclaimer is signed by the assignee (owner). Form PTO/SB/96 may be used for making this statement. See MPEP § 324.

EXHIBIT 7

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent of:	Confirmation No.: 4303
Sherman *et al.*	Art Unit: 1652
U.S. Patent No. 6,783,965	Examiner: Pak, Yong D.
Issued: August 31, 2004	Atty. Docket: 2057.0080000/BJD/SAC
For: **Aggregate-Free Urate Oxidase for Preparation of Non-immunogenic Polymer Conjugates**	

Statutory Terminal Disclaimer Under 35 U.S.C. § 253 and 37 C.F.R. § 1.321(a)

Commissioner for Patents
Washington, D.C. 20231

Sir:

During prosecution of U.S. Appl. No. 09/501,730 which resulted in the issuance of the above-captioned patent, a Terminal Disclaimer was filed by Mountain View Pharmaceuticals, Inc. on December 4, 2003. Subsequent to execution of the Terminal Disclaimer and issuance of the above-captioned patent, inventorship was amended pursuant to 37 C.F.R. § 1.324(a). As a result, the above-captioned patent is now co-owned by Mountain View Pharmaceuticals, Inc. and Duke University. In view of the corrected inventorship, co-owner Duke University encloses an executed Terminal Disclaimer that also is executed by co-owner Mountain View Pharmaceuticals, Inc. Thus, so that the record of the above-captioned patent is clear, the co-owners hereby provide a joint Terminal Disclaimer.

Mountain View Pharmaceuticals, Inc. and Duke University represent that they are the owners of the entire right, title, and interest of U.S. Application No. 09/501,730, filed on February 10, 2000, and U.S. Patent No. 6,783,965 that issued therefrom, by virtue of:

(a) an Assignment from Merry R. Sherman, Mark G.P. Saifer and L. David Williams to Mountain View Pharmaceuticals, Inc. executed on April 26, 2000, recorded on May 22, 2000, at Reel 010836, Frame 0572; and

(b) an Assignment from Michael S. Hershfield and Susan J. Kelly to Duke University executed on May 16, 2006 and May 17, 2006 respectively, recorded on May 24, 2006, at Reel 017663, Frame 0313.

Establishing Right of Assignee to Take Action Under 37 C.F.R. § 3.73(b)

A Statement Under 37 C.F.R. § 3.73(b) establishing the right of the assignee to take action, with regard to the above-identified application and patent was filed for Mountain View Pharmaceuticals, Inc. on May 24, 2006. Additionally, a Statement Under 37 C.F.R. § 3.73(b) establishing the right of the assignee to take action, with regard to the above-identified application and patent, was also filed in the above-captioned matter for Duke University on May 24, 2006.

Terminal Disclaimer

Mountain View Pharmaceuticals, Inc. and Duke University, hereby disclaim, except as provided below, the terminal part of the statutory term of the above-captioned patent which would extend beyond the expiration date of the full statutory term of prior patent No. 6,576,235 as the term of said prior patent is defined in 35 U.S.C. §§ 154 and 173, and as the term of said prior patent is presently shortened by any terminal disclaimer.

The co-owners hereby agree that the above-captioned patent shall be enforceable for and during such period that it and the prior patent are commonly owned. The co-owners further acknowledge that this disclaimer is to be binding upon the grantees, assignees, their successors or assigns.

MPR

In making the above disclaimer, the co-owners do not disclaim the terminal part of the term of the captioned patent that would extend to the expiration date of the full statutory term as defined in 35 U.S.C. §§ 154 and 173 of the **prior patent**, "as the term of said **prior patent** is presently shortened by any terminal disclaimer," in the event that said **prior patent** later:

expires for failure to pay a maintenance fee;
is held unenforceable;
is found invalid by a court of competent jurisdiction;
is statutorily disclaimed in whole or terminally disclaimed under 37 C.F.R. 1.321;
has all claims canceled by a reexamination certificate;
is reissued; or
is in any manner terminated prior to the expiration of its full statutory term as presently shortened by any terminal disclaimer.

The co-owners also do not disclaim any term of the above-captioned patent that is extended pursuant to 35 U.S.C. § 156.

In accordance with 37 C.F.R. § 1.321(a), this disclaimer is accompanied by the fee set forth in 37 C.F.R. § 1.20(d). We have read and understand 37 C.F.R. § 10.18(b).

For: Mountain View Pharmaceuticals, Inc.

Signature: Merry R. Sherman

Type or Print Name: Merry R. Sherman

Title: CEO and President

Date: July 17, 2008

For: Duke University

Signature: [signature]

Type or Print Name: Robert L. Taber, Ph.D.

Title: Vice Chancellor, Corporate & Venture Development

Date: 7/21/07

EXHIBIT 8

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,783,965 B1
APPLICATION NO. : 09/501730
DATED : August 31, 2004
INVENTOR(S) : Sherman et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

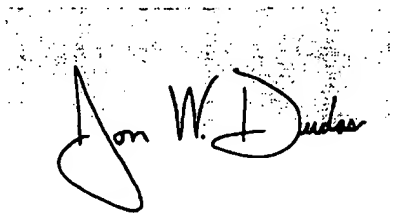
On the Title page, 1st column, please delete Item (75), "Merry R. Sherman, San Carlos, CA (US); Mark G.P. Saifer, San Carlos, CA (US); L. David Williams, Fremont, CA (US);" and insert therein -- Merry R. Sherman, San Carlos, CA (US); Mark G.P. Saifer, San Carlos, CA (US); L. David Williams, Fremont, CA (US); Michael S. Hershfield, Durham, NC (US); Susan J. Kelly, Chapel Hill, NC (US);--

and

In column 18, Line 52-57 please delete claim 8, "The uricase of claim 7, wherein the chimeric uricase is porcine uricase in which arginine residue 291 of SEQ ID NO:2 has been replaced by lysine (R291 K) and threonine residue 301 of SEQ ID NO:2 has been replaced by serine (T301 S) (PKS uricase)." and insert therein --The uricase of claim 7, wherein the chimeric uricase is porcine uricase in which arginine residue 291 of SEQ ID NO:1 has been replaced by lysine (R291 K) and threonine residue 301 of SEQ ID NO:1 has been replaced by serine (T301 S) (PKS uricase). --

Signed and Sealed this

Nineteenth Day of December, 2006



JON W. DUDAS
Director of the United States Patent and Trademark Office

EXHIBIT 9

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,783,965 B1
APPLICATION NO. : 09/501730
DATED : August 31, 2004
INVENTOR(S) : Sherman et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the Title page of the patent, please replace exemplary drawing FIG. 1 with corrected FIG. 1.

Also, please replace FIG. 1 and FIG. 5 with corrected replacement figures attached herein.

Signed and Sealed this

First Day of September, 2009

David J. Kappos

David J. Kappos
Director of the United States Patent and Trademark Office

(12) **United States Patent**
Sherman et al.

(10) **Patent No.: US 6,783,965 B1**
(45) **Date of Patent: *Aug. 31, 2004**

(54) **AGGREGATE-FREE URATE OXIDASE FOR PREPARATION OF NON-IMMUNOGENIC POLYMER CONJUGATES**

(75) Inventors: **Merry R. Sherman**, San Carlos, CA (US); **Mark G. P. Saifer**, San Carlos, CA (US); **L. David Williams**, Fremont, CA (US)

(73) Assignee: **Mountain View Pharmaceuticals, Inc.**, Menlo Park, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **09/501,730**

(22) Filed: **Feb. 10, 2000**

(51) Int. Cl.[7] C12N 9/84; C12N 15/00; A61K 38/44; C07K 1/00; C07H 21/04

(52) U.S. Cl. 435/198; 435/191; 435/440; 424/94.4; 536/23.2; 530/350

(58) Field of Search 435/190, 191, 435/440, 170; 424/94.4, 94.6; 536/23.2; 530/350, 413

(56) **References Cited**

U.S. PATENT DOCUMENTS

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4,460,683	A	7/1984	Ologer et al.	
4,766,106	A	8/1988	Katre et al.	
4,847,325	A	7/1989	Shadle et al.	
4,917,888	A	4/1990	Katre et al.	
5,286,637	A	2/1994	Veronese et al.	435/183
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5,919,455	A	7/1999	Greenwald et al.	
6,376,235	B1 *	6/2003	Williams et al.	424/94.4
2002/0110319	A1 *	1/2002	Ansaldi et al.	530/387.1

FOREIGN PATENT DOCUMENTS

DE	279 486 A1	6/1990
JP	09154581	6/1997
WO	WO 94/19007	9/1994
WO	WO 00/07629	2/2000
WO	WO 00/08196	2/2000

OTHER PUBLICATIONS

Caliceti et al. Biopharmaceutical properties of uricase conjugated to neutral and amphiphilic polymer. Bioconjugate Chem. 10, 638–646. (1999).*

(List continued on next page.)

Primary Examiner—Ponnathapu Achutamurthy
Assistant Examiner—Yong Pak
(74) *Attorney, Agent, or Firm*—Sterne, Kessler, Goldstein & Fox P.L.L.C.

(57) **ABSTRACT**

A naturally occurring or recombinant protein, especially a mutein of porcine urate oxidase (uricase), that is essentially free of large aggregates can be rendered substantially non-immunogenic by conjugation with a sufficiently small number of strands of polymer such that the bioactivity of the protein is essentially retained in the conjugate. Such conjugates are unusually well suited for treatment of chronic conditions because they are less likely to induce the formation of antibodies and/or accelerated clearance than are similar conjugates prepared from protein preparations containing traces of large aggregates.

30 Claims, 6 Drawing Sheets

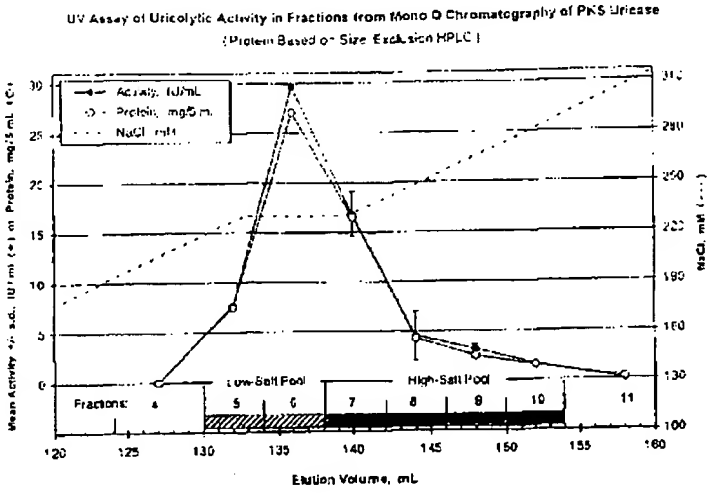


FIG. 1

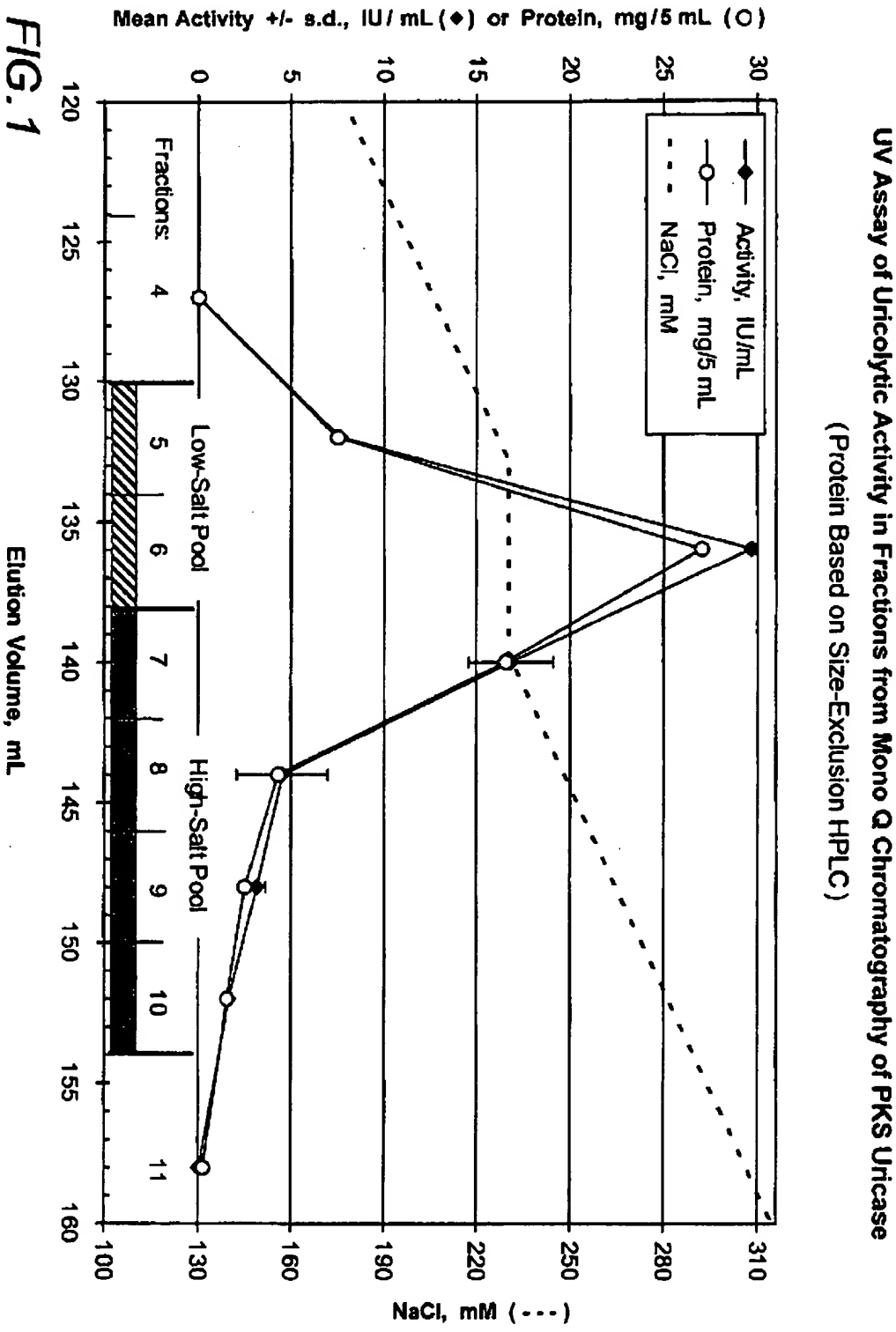
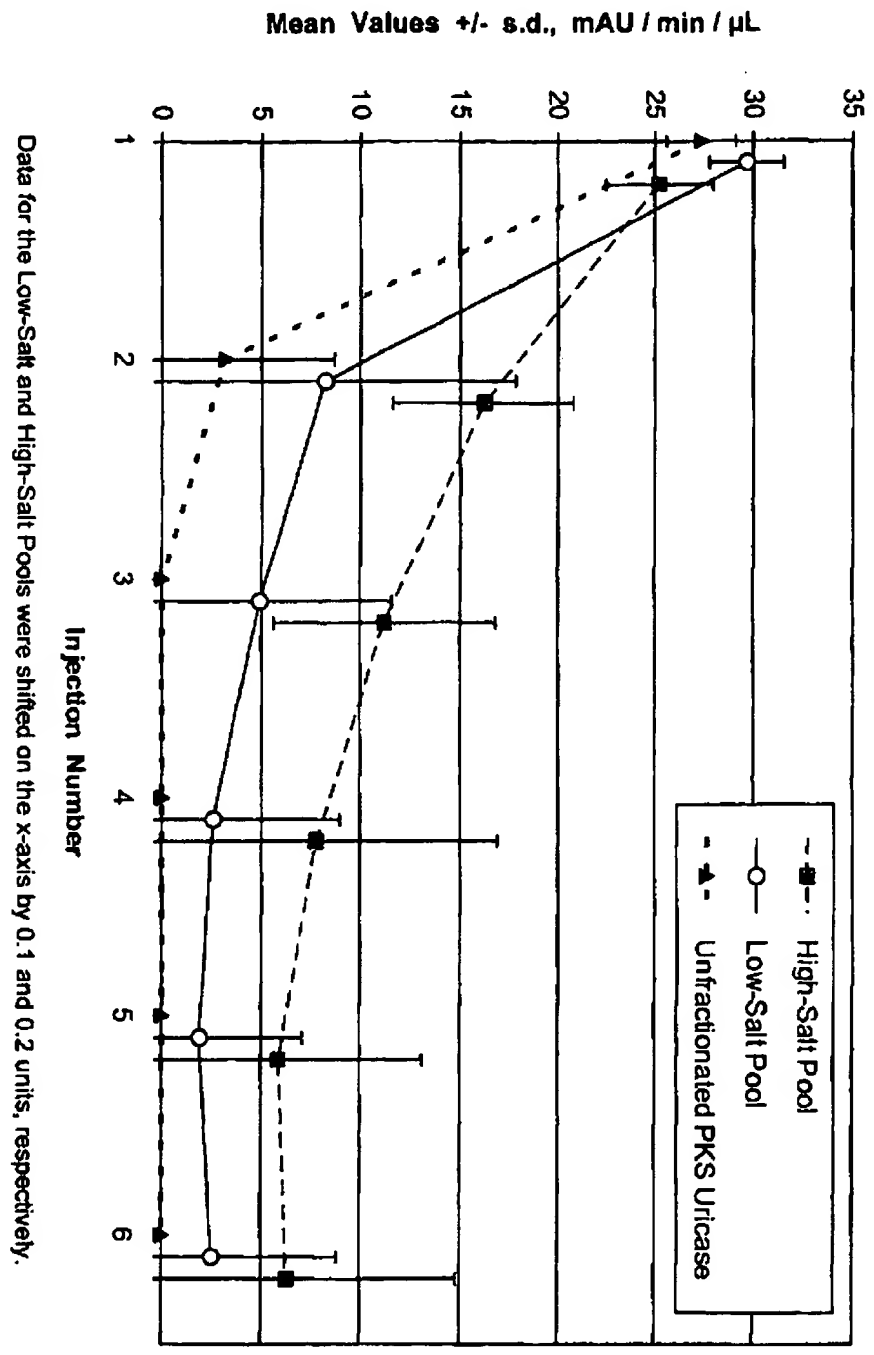

UV Assay of Uricolytic Activity in Fractions from Mono Q Chromatography of PKS Uricase
(Protein Based on Size-Exclusion HPLC)
Mean Activity +/- s.d., IU/mL (◆) or Protein, mg/5 mL (○)
Activity, IU/mL
Protein, mg/5 mL
NaCl, mM
Fractions: 4 5 6 7 8 9 10 11
Low-Salt Pool
High-Salt Pool
Elution Volume, mL
NaCl, mM (- - -)

FIG. 5



UV Uricase Assays of Sera from Mice Injected with 6 x 10-kDa PEG Conjugates of PKS Uricase or of Pools from Mono Q Column Fractions
(Mice Were Bled 24 Hours after Each Weekly Injection.)

Data for the Low-Salt and High-Salt Pools were shifted on the x-axis by 0.1 and 0.2 units, respectively.

EXHIBIT 10

Return To:
USPTO Home Page
Finance Online Shopping Page

United States Patent and Trademark Office

Maintenance Fee Statement

09/20/2010 11:10 AM EDT

Patent Number: 6783965

Customer Number: 26111

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C
1100 NEW YORK AVENUE, N.W.
WASHINGTON DC 20005

According to the records of the U.S.Patent and Trademark Office (USPTO), the maintenance fee and any necessary surcharge have been timely paid for the patent listed below. The "PYMT DATE" column indicates the payment date (i.e., the date the payment was filed).

The payment shown below is subject to actual collection. If the payment is refused or charged back by a financial institution, the payment will be void and the maintenance fee and any necessary surcharge unpaid.

Direct any questions about this statement to: Mail Stop M Correspondence, Director of the USPTO, P.O.Box 1450, Alexandria, VA 22313-1450.

PATENT NUMBER	FEE AMT	SUR-CHARGE	PYMT DATE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	SMALL ENTITY?	ATTY DKT NUMBER
6,783,965	$930.00	$0.00	02/14/08	09/501,730	08/31/04	02/10/00	04	NO	2057.0080000

Click here to obtain your Maintenance Fee Statement as a PDF.
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EXHIBIT 11

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
1401 Rockville Pike
Rockville MD 20852-1448

NOV 3 0 2001

Our Reference: BB-IND 10122

Bio-Technology General Corporation
Attention: Mr. Briti Kundu
Director, Regulatory Affairs
70 Wood Avenue South
Iselin, NJ 08830

Dear Mr. Kundu:

The Center for Biologics Evaluation and Research has received your **Investigational New Drug Application (IND)**. The following product name and BB-IND number have been assigned to this application. They serve only to identify it and do not imply that this Center either endorses or does not endorse your application.

BB-IND #: 10122

SPONSOR: Bio-Technology General Corporation

PRODUCT NAME: Uricase (recombinant, E coli, Bio-Technology General Corp.), PEG Conjugate

DATE OF SUBMISSION: November 15, 2001

DATE OF RECEIPT: November 19, 2001

This BB-IND number should be used to identify all future correspondence and submissions, as well as telephone inquiries concerning this IND. Please provide an **original and two copies of every submission to this file**. Please include three originals of all illustrations which do not reproduce well.

It is understood that studies in humans will not be initiated until 30 days after the date of receipt shown above. If this office notifies you, verbally or in writing, of serious deficiencies that require correction before human studies can begin, it is understood that you will continue to withhold such studies until you are notified that the material you have submitted to correct the deficiencies is satisfactory. If such a clinical hold is placed on this file, you will be notified in writing of the reasons for placing the IND on hold.

You are responsible for compliance with applicable portions of the Public Health Service Act, the Federal Food, Drug, and Cosmetic Act, and the Code of Federal Regulations (CFR). A copy of 21 CFR Part 312, pertaining to INDs, is enclosed. Copies of other pertinent regulations are available from this Center upon request.

The following points regarding obligations of an IND sponsor are included for your information only, and are not intended to be comprehensive.

Progress reports are required at intervals not exceeding one year and are due within 60 days of the anniversary of the date that the IND went into effect [21 CFR 312.33]. Any unexpected, fatal or immediately life-threatening reaction associated with use of this product must be reported to this Division by telephone or facsimile transmission no later than seven calendar days after initial receipt of the information. All serious, unexpected adverse experiences, as well as results from animal studies that suggest significant clinical risk, must be reported, in writing, to this Division and to all investigators within fifteen calendar days after initial receipt of this information [21 CFR 312.32].

Charging for an investigational product in a clinical trial under an IND is not permitted without the prior written approval of the FDA.

Prior to use of each new lot of the investigational biologic in clinical trials, please submit the lot number, the results of all tests performed on the lot, and the specifications when established (i.e., the range of acceptable results).

If not included in your submission, please provide copies of the consent forms for each clinical study. A copy of the requirements for and elements of informed consent are enclosed. Also, please provide documentation of the institutional review board approval(s) for each clinical study.

All laboratory or animal studies intended to support the safety of this product should be conducted in compliance with the regulations for "Good Laboratory Practice for Nonclinical Laboratory Studies" (21 CFR Part 58, copies available upon request). If such studies have not been conducted in compliance with these regulations, please provide a statement describing in detail all differences between the practices used and those required in the regulations.

Item 7a of form FDA 1571 requests that either an "environmental assessment," or a "claim for categorical exclusion" from the requirements for environmental assessment, be included in the IND. If you did not include a response to this item with your application, please submit one. See the enclosed information sheet for additional information on how these requirements may be addressed.

Telephone inquiries concerning this IND should be made directly to me at (301) 827-5101. Correspondence regarding this file should be addressed as follows:

Center for Biologics Evaluation and Research
Attn: Office of Therapeutics Research and Review
HFM-99, Room 200N
1401 Rockville Pike
Rockville, MD 20852-1448

If we have any comments after we have reviewed this submission, we will contact you.

Sincerely yours,

Jeanne M. Delasko

Jeanne M. Delasko, R.N., M.S.
Regulatory Project Manager
Division of Application Review and Policy
Office of Therapeutics
Research and Review
Center for Biologics
Evaluation and Research

Enclosures (3): 21 CFR Part 312
21 CFR 50.20, 50.25
Information sheet on 21 CFR 25.24

EXHIBIT 12

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Our STN: BLA 125293/0

BLA ACKNOWLEDGEMENT

NOV 12 2008

Savient Pharmaceuticals, Inc.
One Tower Center Boulevard
14th Floor
East Brunswick, NJ 08816

Attention: Murad Husain
Vice President of Regulatory Affairs

Dear Mr. Husain:

We have received your biologics license application (BLA) submitted under section 351 of the Public Health Service Act (PHS Act) for the following:

Name of Biological Product: Pegloticase

Date of Application: October 31, 2008

Date of Receipt: October 31, 2008

Our Submission Tracking Number (STN): BL 125293/0

Proposed Use: Intravenous infusion intended for patients with treatment failure gout to control hyperuricemia and to manage the signs and symptoms of gout.

If you have not already done so, promptly submit the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action. The content of labeling must conform to the format and content requirements of revised 21 CFR 201.56-57.

We will notify you within 60 days of the receipt date if the application is sufficiently complete to permit a substantive review.

The BLA Submission Tracking Number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Therapeutic Biological Products Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission.

If you have any questions, call me at (301) 796-4029.

Sincerely,

Diana L. Walker, Ph.D.
Regulatory Project Manager
Division of Anesthesia, Analgesia
and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

EXHIBIT 13

PEG-URICASE®
PRE-IND/IND #10122

INDEX OF APPLICATION CORRESPONDENCES

Date	From	Info Type	Description
8/15/2000	BTG	Initial Submission	**Telephone Call Report** by B. Kundu to W. Aaronson FDA. Pre-IND Meeting Telephone Call
9/22/2000	BTG	Initial Submission	**Letter** to Dr. G. Jones, FDA: Request for a Pre-IND Meeting (Type B Meeting) PEG-Uricase from B. Kundu of BTG
9/22/2000	BTG	Initial Submission	**FAX** from BTGH to Lori Tull FDA - Request for a Meeting, attached copy of the pre-IND meeting request letter dated 9/22/00
9/26/2000	FDA	Initial Submission	**Telephone Call Report** by B. Glasscock FDA taken by M. Califre: Pre-IND Meeting Request
9/28/2000	BTG	Initial Submission	**Telephone Call Report** by B. Kundu to B. Glasscock of FDA. Scheduling of Pre-IND Conference call
10/2/2000	FDA	Initial Submission	**FAX** from B. Glasscock of FDA schedule confirmation of teleconferenc for Nove 13, 2000 to discuss the proposed preclinical and clincal development program
10/3/2000	BTG	Initial Submission	**Telephone Call Report** by M. Califre to FDA B. Glasscock. Confirmation of Receipt of FAX announcing Teleconference Date and Time
10/3/2000	FDA	CMC	**Telephone Call Report** Dr. B. Glasscock FDA to B. Kundu of BTG: FDA pre IND Meeting: CMC
10/12/2000	BTG	Initial Submission	**Letter** to Dr. G. Jones FDA: PEG-uricase Information Package for the Pre-IND Teleconference
11/9/2000	BTG	Initial Submission	**Fax** to B. Glasscock, CSO FDA PEG-uricase, Brief Outline of Presentations for Teleconference to take place today, November 13, 2000 (preIND meeting)
11/13/2000	BTG	Clinical	**Telephone Call Report** B. Kundu: Teleconference: Clinical Questions for the Phase I/II study
11/13/2000	BTG	Clinical	**Telephone Call Report**: Called by Norman barton: M. Califre, et al. Pre-IND teleconference to discuss the proposed preclinical and clinical development program (see attached meeting minutes)
11/13/2000	BTG	Initial Submission	**Letter** to Dr. G. Jones FDA: PEG-uricase...Outline of presentation materials for the Nov 13 2000 Pre-IND Teleconference
11/28/2000	FDA	Clinical	**Telephone Call Report J. Siegel: Returning a Devos' phone call to ask questions pertaining to PEG-uricase Clinical Program**
11/30/2000	BTG	Clinical	**Telephone Call Report:** Clinical Questions for the Phase I/II study; BTG will send an outline of the Phase I/II protocol and additional questions to Dr. Siegel
12/6/2000	FDA	Pharmacology/ Toxicology	**Telephone Call Report J. Siegel:** Response to pre-clinical questions asked by BTG during the telephone conference on 11/30/00
12/8/2000	FDA	Meeting Minutes	**Meeting Minutes**: Fax from FDA about Mtg Minutes Summary of November 13, 2000 meeting held to discuss the proposed Preclinical and Clinical Development Programs.
12/13/2000	BTG	Pharmacology/ Toxicology	**Outlines of Repeated-Dose Toxicity Studies and Phase I/II Clinical Protocol:** Letter to Glen Jones sent via FedEx
12/13/2000	BTG	Pharmacology/ Toxicology	**Outlines of Repeated-Dose Toxicity Studies and Phase I/II Clinical Protocol:** Fax to Jeffrey Siegel
12/13/2000	FDA	Meeting Minutes	**Meeting Minutes:** Receipt of FDA Summary of November 13, 2000 Meeting
12/19/2000	FDA	Correspondence	**Telephone Call Report:** Diane Sartor, Consumer Safety Technician, called to ask for the IND number for the 12/13/00 submission. B. Kundu informed her that we have not yet submitted the IND and the product is in the pre-IND development stage. B. Kundu no
1/4/2001	FDA	Pharmacology/ Toxicology	**Telephone Call Report:** Dr. Martin Green, FDA toxicology reviewer called and informed BTG that the protocol outline for the 56-day repeat dose rat and dog study, submitted on 12/13/00 was acceptable

INDEX OF APPLICATION CORRESPONDENCES

Date	From	Info Type	Description
8/16/2001	BTG	Pharmacology/ Toxicology	**Telephone Call Report:** spoke to Dave(Martin) Green regarding the relevancy of a carcinogenicity study & the specifics of an animal reproduction study.
11/15/2001	BTG	New Protocol	**Serial No. 000: Original IND Application** (our Acknowledgement received 11/19/01)
11/30/2001	FDA	Correspondence	**Serial-000: BB-IND #10122** Acknowledgement Letter – 11/30/01
12/10/2001	BTG	Correspondence	**Serial-000:** Spoke to Jeannie Delasko (Marcy) re: Verify receipt of Puricase IND.
12/11/2001	FDA	Correspondence	**Telephone Call Report:** Dr. Jeffrey Siegel called to introduce himself. He also has a few questions regarding the protocol and would like to set-up a teleconference call for Tuesday, 12/12.
12/11/2001	BTG	Correspondence	**Serial-001: Gen'l Corres** - Notify FDA that Thomas, Marcy and Chris can be contacted regarding IND communications. (acknowledgement receipt 12/12)
12/12/2001	BTG	Correspondence	**E-Mail to Dr. Siegel:** Confirming conference call for Thursday, December 14 at 10am
12/13/2001	BTG	Clinical	**Teleconference to Discuss Questions on Protocol C0401.** Spoke w/Jeffrey Siegel
12/13/2001	BTG	Clinical	**Serial-002: Response to Request for Information** - Reference is made to the 12/13/01 teleconference call w/Dr. Siegel submitting draft copy of the consent form and a list of the protocol revisions.(acknowledgement receipt 12/14)
12/13/2001	BTG	Clinical	**FAX**: to Dr. Siegel "copy of the draft informed consent form for the protocol C0401 along with the list of protocol revisions – 12 pages
12/14/2001	FDA	Correspondence	**Telephone Call Report:** Dr. J. Siegel called to inform BTG that we can proceed with the clinical study C0401
12/18/2001	BTG	Correspondence	**Letter to Marlene Haffner** – Copy of letter to Orphan Products Development Division notifiying them of the filing of aBB- IND for Puricase (acknowledgement receipt 12/20/01 by Jeff Fritsch)
1/10/2002	FDA	Correspondence	**Telephone Call Report: w/Jeannie Delasko**: Schedule Teleconference to discuss proposed clinical reproduction studies with FDA preclinical reviewer
1/10/2002	BTG	Correspondence	**Telephone Call Report: w/Lauren Black** – Schedule Teleconference to discuss proposed preclinical reproduction studies with FDA preclinical reviewer
1/18/2002	FDA	Clinical	**FDA letter from Glen Jones :** Comments on IND submission: Agreement that C0401 study may proceed. Comments on CMC section of IND and request for additional CMC information during development, including submission of C of As for bulk drug substance and d
1/25/2002	BTG	Protocol Amendments	**S-003:** Submitted **Protocol Amendment No. One**, dated January 22, 2002 (receipt acknowledgement 1/28/02)
1/31/2002	BTG	Clinical	**S-004: Response to FDA Request for Information:** Submitted a copy of the approved informed consent form as well as documentation of IRB approval of the amended protocol. (our Acknowledgement received 02/02/02)
2/6/2002	BTG	Clinical	**S-005: Revised 1572** to include sub investigator, change of IRB address and addition of Dr. Herschfield's lab (for information only not a clinical lab) receipt acknowledgement 2/7
2/8/2002	FDA	Clinical/Tox	**Letter from FDA - Glen D. Jones**: received our IND and have the following comments and requests for information regarding our pre-clinical toxicology program
2/8/2002	BTG	Clinical/Tox	**Fax to Dr. Lauren Black:** Request for a teleconference to discuss proposed preclinical program; background material attached includes description of proposed preclinical program and summary of planned clinical program.

PEG-URICASE®
PRE-IND/IND #10122

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Date	From	Info Type	Description
2/8/2002	BTG	Clinical/Tox	**S-006: Response to Request for Information** - Submissionof preclinical background information requested in preparation for upcoming teleconference to discuss the proposed preclinical program for Puricase. This information was previously faxed to Lauren B
2/11/2002	FDA	Correspondence	**Telephone Call Report:** from Lauren Black to schedule a telephone conference
2/11/2002	BTG	Correspondence	E-Mail to Dr. Black confirming if she received our fax on 2/7
2/12/2002	FDA	Correspondence	**Telephone Call Report**: w/Lauren Black and Marcy Califre: schedule teleconference to discuss proposed preclinical reproduction studies with FDA preclinical reviewer.
2/12/2002	FDA	Pharmacology/ Toxicology	**E-Mail**: Reply via e-mail from Dr. Black confirming conference call for Thursday 2/14 @ 9:00 am
2/12/2002	BTG	Pharmacology/ Toxicology	**E-mail to Dr. Black:** Change in date for teleconference call instead of Friday, have it Thursday, 2/14/01?
2/12/2002	BTG	Meeting Minutes	**E-mail to Dr. Black:** Minutes from FDA-BTG Pre-IND Meeting/Teleconference held on 11/13/00
2/12/2002	FDA	Correspondence	**E-mail from FDA:** Dr. Black confirming receipt of 15 page fax sent to her
2/13/2002	BTG	Correspondence	**E-Mail to Dr. Black**: Confirming conference call and list of attendees from BTG Corp. and BTG (Israel)
2/14/2002	BTG	Pharmacology/ Toxicology	**Telephone Call Report**: w/Lauren Black (FDA), Norman Barton, Marcy Califre, Arjen DeVos, Rami Nimrod, Rivka Zaibel on 2/14/02. **Subject**: Discuss Proposed Preclinical Program for Puricase™ with FDA Preclinical Reviewer. 9AM.
2/14/2002	FDA	Pharmacology/ Toxicology	**Telephone Call Report** from Dr. Lauren Black: Carcinogenicity Study: FDA Telephone Call. As a follow-up to the teleconference call held today 2/14 @ 9:00 am, Dr. Black responded to BTG's question regarding the requirement of the carcinogenicity study for
3/19/2002	BTG	Clinical/Tox	**S-007 Response to FDA Request for Information:** (acknowledgement receipt 3/20/02), Response to questions posed in 2/8/02 FDA letter provided; revised IB, IC and revised C0401 protocol (amendment # 2) were submitted along with responses and commitments to
3/26/2002	BTG	CMC	**S-008**: **Response to FDA for Information**: Response to FDA letter dated 1/18/02 regarding chemistry, manufacturing & controls development plans. (acknowledgement received 03/27/02)
4/2/2002	BTG	Pharmacology/ Toxicology	**S-009**: **Information Amendment**: As a follow up of the commitment noted in S#007 for submission of additional histopath information from dog study, amendment 1 to the final study report, #20-2-0189-00, entitled 'Repeated Dose Toxicity of "Puricase" in the D
4/18/2002	BTG	IND Safety Reports	**S-010**: **IND Safety Report:** Gout attack with draining tophus; Initial Report: Patient # 001-007 MDD (Dr. Sundy's site)
4/23/2002	BTG	Correspondence	**E-mail to Dr. Siegel** re: Protocol C0401 Issue to Discuss – Conference Call 4/24/02?
4/24/2002	BTG	Pharmacology/ Toxicology	**Fax to Andrea Weir**, new toxicologist for PEG. 27 pages fax to AW re: Pharmacology and Toxicology section from the IND for her review.
4/24/2002	FDA	Pharmacology/ Toxicology	**Telephone Call Report** w/Andrea Weir, Toxicologist from FDA phoned to discuss 'Proposed IV Dosing'
4/24/2002	BTG	Correspondence	**E-mail to Dr. Siegel** re: Protocol C0401 Issue to Discuss – Conference Call confirmation date – May 6th
4/24/2002	FDA	Correspondence	**E-mail from Dr. Siegel** re: Protocol C0401 Issue to Discuss – Conference Call alternative date – May 6th
4/25/2002	BTG	Clinical	**S-011 General Correspondence**: Notification to FDA of suspension of dosing in C0401 study(acknowledgement receipt 4/26/02)
4/30/2002	BTG	Correspondence	**E-mail from Marcy to Dr. Siegel**: Confirmation of teleconference to discuss Puricase BB-IND 10122 – Current Issues

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Date	From	Info Type	Description
5/2/2002	BTG	Correspondence	**E-mail from Marcy to Dr. Siegel**: confirming conference call – confirmation of new time
5/2/2002	FDA	Correspondence	**E-mail from Dr. Siegel**: confirming conference call – change of time
5/3/2002	FDA	Correspondence	**E-mail from Dr. Siegel** – confirming telephone number and the name of the allergist
5/3/2002	BTG	Correspondence	**E-mail to Dr. Siegel** – confirming telephone number for MCI
5/3/2002	BTG	Clinical	**Telephone Call Report with Dr. Siegel** – May 6th conference call attendees
5/6/2002	BTG	Clinical	**Telephone Call Report** (conference call) w/J. Siegel/A. Weir/D. Green: Discuss the status of protocol C0401 and BTG plans for pursuing intravenous dosing with Puricase (participants: N. Barton, M. Califre, A. DeVos, T. Eckhardt; A. Nimrod (was disconnecte
5/6/2002	BTG	Correspondence	**E-mail to Dr. Siegel** – teleconference today – attendees
5/7/2002	BTG	Clinical	**S-012 General Correspondence**: Notification of termination of C0401 study. Acknowledgement receipt 5/8/02
5/13/2002	BTG	Correspondence	**General Correspondence** - Letter to Dr. Kathyrn C. Zoon and Theresa Toigo Response to FDA letter regarding the clinical trials data bank
5/13/2002	BTG	Correspondence	**S-013: General Correspondence**: response to FDA letter regarding the clinical trials data bank (our acknowledgement received 05/15/02)
6/5/2002	BTG	Correspondence	**FAX:** Fax to Dr. Weir, a copy of S 014.
6/5/2002	BTG	Correspondence	**S-014: Response to FDA Request for Information** - During the May 6 teleconference, it was suggested that we submit the draft protocol for our subchronic toxicity study via the intravenous route in dogs for FDA review and comments. A copy of this draft pr
6/7/2002	FDA	Clinical	**Telephone Call Report**: PEG-Uricase – Call from Dr. Siegel (FDA) w/BK – received an informal call from Dr Siegel to discuss the abandoned subcutaneous protocol
6/12/2002	BTG	Pharmacology/ Toxicology	**Telephone Call Report-** w/Dr. Siegel, Marcy Califre to discuss Draft Toxicology Protocol for Repeated Dose IV Dog Study.
6/12/2002	BTG	Clinical	**Telephone Call Report** w/Dr. Siegel, Marcy Califre and Arjen DeVos: Respond to Dr. Siegel's question regarding the termination of the C0401 protocol
6/18/2002	BTG	Pharmacology/ Toxicology	**E-mail** to Dr. Weir from MC re: Comments on Toxicology Protocol
6/19/2002	FDA	Pharmacology/ Toxicology	**E-mail** from Dr. Weir to MC re: Comments on Toxicology Protocol (response)
6/20/2002	FDA	Pharmacology/ Toxicology	**Telephone Call Report** w/Dr. Weir and BK re: Draft Toxicology Protocol for Repeated Dose IV Dog Study – Teleconference
6/20/2002	BTG	Pharmacology/ Toxicology	**E-mail** from BK to Dr. Weir re: Comments on Toxicology Protocol (3rd response)
6/21/2002	FDA	Pharmacology/ Toxicology	**Telephone Call Report** w/Dr. Siegel and BK re: Product Reviewer's comments
6/21/2002	BTG	Correspondence	**E-mail** to Dr. Weir re: Confirmation of telephone conference call for Monday 6/24/02 @ 10:00am
6/24/2002	BTG	Pharmacology/ Toxicology	**Telephone Call Report**: conference call held on 6/24 w/Dr. Weir, BK, Mcalifre and R. Nimrod to discuss the draft 12 week IV, Subchronic toxicity protocol in dogs that submitted to FDA on June 5, 2002.

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Date	From	Info Type	Description
6/24/2002	FDA	Correspondence	**E-mail** from Dr. Weir with recommendation for re: 'recovery + challenge" issues with David Green
6/24/2002	FDA	Pharmacology/ Toxicology	**E-mail** from Dr. Weir re: Comments on Toxicology Protocol – Conference Call Confirmation time
7/3/2002	BTG	Pharmacology/ Toxicology	**E-mail to Dr. Weir:** BK sent the revised protocol via telefax and enclosing a copy of the same protocol & cover fax in addition to faxing it, it's also being e-mailed
7/3/2002	BTG	Protocol Amendments	**FAX: Revised protocol**: 12-week Repeated Dose Intravenous Injection Toxicity Study with Puricase in dogs (20 pgs), which included FDA recommendations, was faxed to Dr. Weir
7/8/2002	BTG	Correspondence	**E-mail to Dr. Weir:** regarding question if BTG plans to submit an official copy of 12 week dog study protocol to the submission? BK's response is yes we plan to submit a signed hard copy of the protocol to the IND
7/8/2002	FDA	Correspondence	**E-mail from Dr. Weir:** Confirmation receipt of e-mail and fax of revised protocol (sent 07/03/02)
7/23/2002	BTG	Correspondence	**Fax to Dr. Siegel re**: Proposed Protocol for Skin Test would like to discuss further at his convenience
7/24/2002	BTG	Pharmacology/ Toxicology	**S-015**: **Final protocol**: (study identification: Covance 6432-106) for the study '12 week repeated dose intravenous injection toxicity study with Puricase' (our acknowledgement received 07/26/02)
7/31/2002	BTG	Clinical	**E-mail to Dr. Siegel:** Outline for Skin Testing; what is the status of 7/23 faxed of the outline skin testing?
8/1/2002	BTG	Clinical	**S-016: Response to FDA Request for Information:** Highlights of May 15, 2002 Expert Meeting discussing immunogenicity and adverse reactions in the C0401 subcutaneous study
8/16/2002	BTG	Correspondence	**E-mail** to Dr. Siegel: Schedule a conference call to discuss the skin test outline.
8/19/2002	FDA	Correspondence	**E-mail** from Dr. Siegel: Response to conference call which has been confirmed for 8/27 @ 2:00pm.
8/21/2002	BTG	Correspondence	**E-mail** to Dr. Siegel confirming per his request, the new time for the conference call to discuss the 'skin test outline'.
8/27/2002	BTG	Correspondence	**Telephone Report** w/Dr. Siegel, Dr. Esayan (consulting immunologist), Arjen and BK to discuss the skin test protocol outline
9/9/2002	BTG	Clinical	**S-017**: **Protocol Amendment: Change in Protocol** Submitted documentation of IRB approval of C0401 Amendment #2 and IRB approval of the revised informed consent form per FDA request. A copy of the approved informed consent form was also submitted. (Acknow
9/30/2002	BTG	Clinical	**S-018: Information Amendment: Clinical**-Submit revised FDA 1572 form for Dr. Sundy adding Rex McCallum as a sub investigator (acknowledgement receipt 10/02/02)
10/1/2002	BTG	New Protocol	**S-019**: Protocol Amendment: New Protocol. Submit draft C0402 Phase I IV study protocol for review and comments. Dr. John Sundy, PI. (Acknowledgement receipt 10/2/02)
10/22/2002	BTG	Correspondence	**E-mail to Dr. Seigel:** Review of draft protocol C0402 interested to hear the comments
10/28/2002	BTG		**Telephone Call Report:** w/Dr. Siegel to discuss Confirmation of Teleconference: Nov. 5th at 4:00 pm
10/28/2002	BTG		**E-mail to Dr. Siegel:** Confirming Conference Call
10/28/2002	FDA		**E-mail from Dr. Siegel:** Schedule conference Call
10/29/2002	BTG	Correspondence	**E-mail from Dr. Siegel**: regarding new time for Conference Call
10/29/2002	BTG	Correspondence	**Serial #020: General Correspondence: Sponsor Change of Address** –letter sent to Dr. Jones with new address/phone and fax #
10/29/2002	BTG	Correspondence	**E-mail to Dr. Siegel** confirming new date and time of conference call

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11/7/2002	FDA	Correspondence	**E-mail from Andrea Weir:** regarding availability of the week of 11/18 to discuss the animal data.
11/7/2002	BTG	Correspondence	**E-mail to Andrea Weir:** regarding a telephone conf. Call to discuss I.V. dog study and need her input regarding the submission of the available data
11/14/2002	BTG	Clinical	**SN 021 - Information Amendment: Clinical** we are amending our IND to include a revised Investigator's Brochure; Version 3 dated November 8, 2002. The IB was revised to include pharmacokinetic and safety information from our C0401 Phase I, subcutaneous cli
11/14/2002	BTG	Correspondence	**E-mail to Andrea Weir:** regarding draft preclinical toxicity report
11/19/2002	BTG	Pharmacology/ Toxicology	**E-mail to Dr. Weir:** Confirmation of 11/20/02 conference call along a list of the attendees and attachments of what will be discussed, 1) protocol 2) introductory statement and a summary table delineating the study that is available at this time.
11/20/2002	BTG	Pharmacology/ Toxicology	**Telephone Call Report:** with Dr. Weir, Marcy Califre, Arjen DeVos, Rami Nimrod and Shoshi Katz re: Ascertain whether the types of data currently available from 12-week iv, subchronic toxicity dog study, will be sufficient for FDA to determine the advisabil
11/20/2002	BTG	Pharmacology/ Toxicology	**E-mail to Dr. Weir:** forwarded an updated version of the summary table sent to Dr. Weir on 11/19
11/26/2002	BTG	Pharmacology/ Toxicology	**SN 022 - Information Amendment: Pharmacology/Toxicology:** submitting a copy of the interim summary report for Covance protocol 6432-106. All available individual animal data as well as all available summary data are included in this submission. To facil
12/3/2002	BTG	Correspondence	**Telephone Report:** Spoke to B. Friedman to determine the mechanism for obtaining a user fee waiver for BLA due to orphan drug status.
12/10/2002	BTG	Correspondence	**Telephone Report:** Call to A. Weir to determine status of review of interim dog toxicity report submission.
12/10/2002	BTG	Correspondence	**E-mail was sent to Dr. Weir from MC regarding IV Dog Toxicity Interim Report.** Follow-up on the status of submission Serial #022.
12/11/2002	FDA	CMC	**E-mail from Dr. Weir regarding status of Serial #022.** Dr. Weir just received our submission and it has not been reviewed yet however she'll do her best to get to it in the next couple of weeks.
1/7/2003	FDA	CMC	**E-mail from Dr. Weir regarding status of Serial #022.** Dr. Weir responded by stating she did review the study and has a couple of points to discuss with branch chief. She will be discussing these issues with him on 1/08/03 and will
1/7/2003	BTG	CMC	**E-mail to Dr. Weir regarding status of Serial #022:** Dr. Weir needs to discuss a few point with her Branch Chief.
1/8/2003	FDA	CMC	**E-mail from Dr. Weir regarding her completion of her review for study serial #022.** The data in the toxicology study is adequate to support our proposed clinical trial. However, she has one question that needs to be answered: If antibodies are detected i
1/14/2003	BTG	CMC	**Serial #023: Information Amendment: Chemistry /Microbiology:** the following documents were submitted to the FDA:
1/14/2003	BTG	CMC	**Telephone Report w/Dr. Weir:** left a message for Dr. Weir in response to the question posed in her 1/8/03 e-mail.

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Date	From	Info Type	Description
2/12/2003	BTG	New Protocol	**Serial #025: Protocol Amendment: New Protocol: New Investigator** submitted the final C0402 protocol as well as Amendment #1 (dated 2/04/03) to this protocol. Also included in this submission is a signed 1572 form from a C.V. for John Sundy, Principal Inves
2/12/2003	BTG	Annual Report	**Serial #024: Annual Report** covering periods: 12/15/01 – 12/15/02 (acknowledgement receipt 2/13/03)
3/4/2003	BTG	Clinical	**Serial #026: Response to Request for Information:** At this time in accordance with the request made in your letter dated 11/20/01, we are submitting documentation of IRB approval for this protocol and informed consent form. (Acknowledgement received 03/0
4/1/2003	BTG	Protocol Amendments	**Serial #027: Protocol Amendment:** submission of Amendment #2 to Protocol C0402 (acknowledgement received 04/02/03)
5/20/2003	BTG	Correspondence	**Telephone Call Report:** Dr. Siegel advising that the PEG IND will remain with the same FDA reviewers after the transfer from CBER to CDER
6/12/2003	BTG	Correspondence	**Serial #028: General Correspondence:** Change of medical monitor from Ted Kramer to Zeb Horowitz. (Acknowledgement received 06/16/03)
6/17/2003	BTG	Clinical	**Serial #029: Response to Request for Information:** Submission of IRB approval and ICF for Amendment # 2 per FDA 11/03/01 letter. (Acknowledgement received 06/23/03)
6/20/2003	BTG	Correspondence	**Serial # 030: General Correspondence:** Sponsor Change of Name to Savient Pharmaceuticals, Inc. (acknowledgement received 06/30/03)
8/4/2003	Savient	Protocol Amendments	**Serial #031: Protocol Amendment:** Amendment #3; Protocol C0402 (IRB Approval/ICF) (acknowledgement received 08/05/03)
8/18/2003	Savient	Clinical	**Serial #032: Final Clinical Study Report,** Protocol C0401 (acknowledgement received 08/19/03)
9/15/2003	SPI	Clinical	**Serial #033: list of adverse events** from C0402 for orphan drug application for Dr. Michael Hershfield (our acknowledgement received 09/17/03)
9/26/2003	FDA	Correspondence	**Telephone Call Report:** Andrea Weir phoned to inquire if the final report for beagle dogs had been forwarded
10/6/2003	SPI	Correspondence	**Telephone Call Report:** Inquiry regarding new FDA Office of Biotechnology Products/Division of Therapeutic Proteins
10/8/2003	FDA	Correspondence	**Telephone Call Report:** Advisory Committee Meeting for development of products for gout
10/13/2003	SPI	Correspondence	**Background Information** for Arthritis Drug Advisory Committee Meeting on November 13, 2003
10/14/2003	SPI	Pharmacology/ Toxicology	**Serial #034: Information Amendment:** Pharmacology/Toxicology – Submission of final study report for 6432-106, 12-Repeated Dose IV Injection Tox Study with Puricase in Dogs and supporting TK, complement, immunogenicity and Puricase activity study reports.
10/14/2003	FDA	CMC	**Telephone Call Report:** from Kathleen Reedy informing SPI that the Advisory Drug Committee Meeting is being postponed until the first of next year, 2004
10/20/2003	SPI	Clinical	**Serial #035: General Correspondence:** presentation for the Arthritis Drug Advisory Committee Meeting
12/2/2003	SPI	CMC	**Serial # 036: Information Amendment: Chemistry/Microbiology:** Submission of Certificate of Analysis for Puricase lot # 26890051 to be used in C0403 clinical study (our acknowledgement received 12/03/03)
1/21/2004	SPI	Pharmacology/ Toxicology	**Serial #037: Information Amendment: Pharm/Tox:** Draft Toxicology Protocol for 39 week dog study and supporting documents: Protocol C0402 Preliminary PK Data and minutes from FDA pre-IND Meeting 11-13-00

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1/26/2004	SPI	Clinical	**Telephone Report:** Registration of C0403 Phase 2 study with the Clinical Trials Data Bank
2/9/2004	FDA	Correspondence	**Email** - Puricase BB-IND 10122; Request for teleconference to discuss toxicology protocol submitted in Serial # 37 on Jan. 21, 2004
2/12/2004	SPI	Annual Report	**Serial #038 – Annual report** covering the time period of 12/16/2002 – 12/31/2003 (acknowledgement received 02/20/04)
2/18/2004	SPI	Protocol Amendments	**Serial #039: Protocol Amendment:** submission of Amendment to Protocol C0403 (acknowledgement received 02/13/04)
2/19/2004	SPI	Correspondence	**E-mail to Dr. Weir** Puricase BB-IND 10122; Feb 25, 2004 teleconference Agenda to discuss toxicology protocol submitted in Serial # 37 on Jan. 21, 2004
2/24/2004	SPI	Pharmacology/ Toxicology	**E-mail: Dr. Weir** Puricase BB-IND 10122; Feb 25, 2004 teleconference to discuss toxicology protocol submitted in Serial # 37 on Jan. 21, 2004
2/25/2004	SPI/ FDA	Pharmacology/ Toxicology	**Telephone Report:** Teleconference with Dr. Weir Puricase BB-IND 10122; Feb 25, 2004 Agenda to discuss toxicology protocol submitted in Serial # 37 on Jan. 21, 2004
2/25/2004	SPI	Correspondence	**Fax: Dr. Gibbes** Puricase BB-IND 10122; Feb 25, 2004 teleconference (Puricase Activity Method)
2/25/2004	SPI	Pharmacology/ Toxicology	**Serial #040: Information Amendment:** submission of Amendment Pharmacology / Toxicology (acknowledgement received 03/01/04)
4/16/2004	SPI	New Investigator	**Serial #041: Protocol / Information Amendment:** submission of Amendments New Investigators and Clinical (acknowledgement received 04/22/04)
4/30/2004	SPI	Correspondence	**Telephone Report:** June 2-3 Arthritis advisory Committee Meeting
5/10/2004	SPI	New Investigator	**Serial #042: Protocol / Information Amendment:** submission of Amendments New Investigators and Clinical (acknowledgement received 05/18/04)
5/18/2004	SPI	Correspondence	**Serial #043:** General Correspondence: presentation for the Arthritis Drug Advisory Committee Meeting (Acknowledgement received 06/01/04)
6/3/2004	SPI	New Investigator	**Serial #044: Protocol / Information Amendment:** submission of Amendments New Investigators and Clinical (acknowledgement received 06/08/04)
6/23/2004	SPI	IND Safety Reports	**Serial #045: IND Safety Report:** 15 –Day Alert Report for pt. 006-002 – hypersensitivity reaction.(acknowledgement received 07/01/04)
7/8/2004	SPI	IND Safety Reports	**Serial #045/046: IND Safety Report:** 15 –Day Alert Report for pt. 006-001—aggravated gout (acknowledgement received 07/14/04) Serial number correction on 07/15/04(Acknowledgement Received 07/21/04)
8/13/2004	SPI	IND Safety Reports	**Serial # 047: IND Safety Report:** General Correspondence.- Summary Serious Adverse Event and Safety Information from the study C0403 sent to IRBs submitted to FDA.(acknowledgement received 08/13/04)
9/7/2004	SPI	IND Safety Reports	**Serial #048: IND Safety Report Follow-up:** Follow-up information for pt. 006-001 submitted (acknowledgement received 09/13/04)
9/21/2004	SPI	New Investigator	**Serial #049: Protocol/Information Amendment:** submission of Dr. Furie, PI to CO403 Protocol
10/12/2004	SPI	IND Safety Reports	**Serial #050: IND Safety Report Follow-ups:** Administrative changes to Mfr. Reports C0403-0001 and C0403-0002 submitted. 10/12/04 (acknowledgement received 11/02/04)
10/15/2004	SPI	New Investigator	**Serial #051: Information Amendment/ Protocol Amendment:** Submit Amendment #1 to protocol C0403 with IRB approval from Becker's site. (Acknowledgement received on 10/21/04). 10/15/04
11/2/2004	SPI	IND Safety Reports	**Serial # 052: IND Safety Report:** Initial Report-15 Day Alert Report for Pt.# 002-001(Dr. Becker's site)- anemia. 11/2/04

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2/1/2005	SPI	Protocol Amendments	**Serial # 053: Protocol/Information Amendment:** Submission of amended 1572 forms for Dr. Krohn, Baraf, Barkhuizen, Becker, and Moreland to include new lab; submission of documentation for Mountain States Health Laboratory. (Our Acknowledgement Received 2/1
2/22/2005	SPI	Annual Report	**Serial # 054: Annual Report** Covering the period January 1, 2004-December 31, 2004. (Our Acknowledgement Received 3/4/05).
3/3/2005	SPI	Protocol Amendments	**Serial # 055: Protocol Amendment: New Investigator, Information Amendment :** Submission of revised FDA 1572 forms for C0402 PIs Sundy, Kavanaugh and Furie
4/13/2005	FDA	Correspondence	**Telephone Report:** Dr. James Reese, CSO from the FDA called and referenced the letter we sent on April 15, 2005 requesting to reserve a date for EOP2 meeting. He noted that he needed a formal letter with the discussion points and questions in order to sc
4/15/2005	SPI	Correspondence	**Serial # 057: General Corres.** Request to reserve a date for the End-of-Phase 2 meeting date in mid-July, before the review division's calendar gets filled for that month. (Our Acknowledgement Received on 4/26/05).
4/15/2005	SPI	Clinical	**Serial #056: Information Amendment:** Clinical-Submission of Clinical Study Report C0402 (Our Acknowledgement Received on 4/26/05).4/15/05
4/19/2005	SPI	Correspondence	**Telephone Report:** Dr. James Reese, CSO from the FDA called and referenced the letter we sent on April 15, 2005 requesting to reserve a date for EOP2 meeting. He noted that he needed a formal letter with the discussion points and questions in order to sc
4/21/2005	SPI	Correspondence	**Serial # 058: General Corres.** Request to reserve a date for the End-of-Phase 2 meeting date in mid-July, before the review division's calendar gets filled for that month. (Our Acknowledgement Received on April 29, 2005).
5/5/2005	FDA	Correspondence	**Fax:** From FDA re Grants EOP 2 Meeting on July 26, 2005. 5/5/05
5/26/2005	FDA	Clinical	**Telephone Report:** Called Dr. Hull to discuss the requirements of QT/QTc studies for biologics. Dr. Hull noted that CBER never required such a study. He noted that such a study will not be required for Puricase as this is a very large molecule. He reco
6/21/2005	SPI	Briefing Book	**Serial # 059: General Corres** Per the FDA's telefax received on May 5, 2005, we've amended the IND to submit **eleven** copies of the Information Package for the End of Phase 2 Meeting on July 26, 2005 to Dr. Glen Jones, Director, and **three** copies were sent to
6/27/2005	SPI	Correspondence	**Telephone Report:** Dr. James Reese (CSO) confirmed receipt of EOP 2 meeting information package. The division will try to send questions/comments prior to the EOP 2 meeting on July 26, 2005. 6/27/05
7/5/2005	SPI	Clinical	**Telephone Report:** Jeff Fritsch from the FDA made an Inquiry regarding a Compassionate Use Study for PEG. 7/5/05
7/26/2005	SPI	Briefing Book	**Meeting Slides:** Presented at the FDA Meeting on July 26, 2005 in Rockville, MD for the EOP2 Meeting. 7/26/05
7/26/2005	SPI	Briefing Book	**Fax:** Dr. James Reese, PhD forwarded his 2nd draft of questions/comments prior to the EOP 2 meeting on July 26, 2005. 7/26/05
8/5/2005	SPI	Clinical	**Fax:** To Dr. Jeffrey Siegel requesting for review and input of proposal for phase 3 study plan. Savient needs to make a decision between two options for design of the pivotal trials, and cannot proceed to elaborate the Protocols in the absence of a deci

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8/15/2005	FDA	Clinical	**Telephone Call Report:** During the August 15th telephone conference, Dr. Jeffrey Siegel made comments on the phase 3 clinical development: Pivotal Trial Design.
8/16/2005	FDA	Clinical	**Fax:** Dr. James Reese, PhD forwarded a copy of his Memorandum of the July 26, 2005 FDA Meeting. Discuss CMC, Nonclinical and clinical issues relative to Phase 3 dev. 8/16/05
10/12/2005	SPI	Correspondence	**Telephone Call Report:** To Pratibha Rana, CSO regarding the submission of the draft phase 3 protocol.
10/13/2005	SPI	New Protocol	**Serial # 060: Protocol Amend** - Reference is made to the End of Phase 2 Meeting of July 26, 2005 (FDA Minutes dated August 16, 2005), submission of two Phase 3 development scenarios dated August 5, 2005, and a teleconference with Dr. Jeffery Siegel on Aug
10/14/2005	FDA	Correspondence	**Email:** From Pratibha Rana in reference to forwarding the draft Phase 3 Protocol to Dr. Siegel. 10/14/05
10/18/2005	SPI	Correspondence	**Email:** From Marcy Califre to FDA-Rosemarie Neuner regarding change in contact information at Savient Pharmaceuticals, Inc. 10/18/05
10/18/2005	SPI	Correspondence	**Email:** From Marcy Califre to FDA-James Reese regarding change in contact information at Savient Pharmaceuticals, Inc. 10/18/05
10/18/2005	SPI	Correspondence	**Email:** From Marcy Califre to FDA-Andrea Weir regarding change in contact information at Savient Pharmaceuticals, Inc. 10/18/05
10/18/2005	SPI	Correspondence	**Email:** From Marcy Califre to FDA-Pratibha Rana regarding change in contact information at Savient Pharmaceuticals, Inc. 10/18/05
10/18/2005	SPI	Correspondence	**Email:** From Marcy Califre to FDA-Jeffrey Siegel regarding change in contact information at Savient Pharmaceuticals, Inc. 10/18/05
10/27/2005	SPI	Correspondence	**SN061 General Correspondence: Change in contact person.** New contact at Savient Pharmaceuticals, Inc. is Murad Husain. (Our acknowledgement received on 11/3/05)
11/3/2005	FDA	Correspondence	**Email: From FDA-Prathiba Rana to Murad Husain regarding the submission of the SPA.**
11/8/2005	SPI	Clinical	**SN062 General Correspondence-Rationale Document for Phase 3** Protocol Design. (Our Acknowledgement received on 11/17/05)
11/8/2005	SPI	Clinical	**Email:** From Murad Husain to FDA – Pratibha Rana Submission SN062: General Correspondence-Rationale Document for Phase 3 Protocol Design.
11/8/2005	SPI	Correspondence	**Email:** From Murad Husain to FDA - Pratibha Rana regarding the submission of the Rationale document. 11/08/05
11/29/2005	FDA	Clinical	**Email:** From FDA-Pratibha Rana to Murad Husain the response to the draft SPA. The agency has several recommendations to the protocol that they want us to consider incorporating into the final submission.
12/12/2005	SPI	Clinical	**SN063 Request for Special Protocol Assessment-Clinical**
12/13/2005	SPI	Clinical	**Email:** Pratibha Rana's email request to forward the SPA desk copy to FDA Division of Anesthesia, Analgesia, and Rheumatology Products, 10903 New Hampshire Avenue. Bldg 22 Room: 3163, Silver Spring, MD 20903-0002.

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12/13/2005	SPI	Correspondence	**Email:** Response from Murad Husain to FDA-Pratibha Rana regarding her request to forward Desk Copy of 12/12/05 Submission SN063- Request for special Protocol Assessment-Clinical to her new address in Silver Springs, MD. An electronic copy of the cover le
12/13/2005	FDA	Response to FDA Request for Information	**Email:** From Pratibha Rana to Murad Husain to acknowledge FedEx tracking of Desk Copy
12/13/2005	SPI	Correspondence	**Fax:** Cover Letter of Submission SN063-Request for Special Protocol Assessment from Murad Husain to Pratibha Rana. Fax included 9 pages.
12/13/2005	SPI	Correspondence	**Email:** From Murad Husain to FDA-Pratibha Rana informing her that we have sent out the SPA on 12/12/05 via overnight express mail which included a desk copy for her in the package.
12/19/2005	SPI	Clinical	**Email:** Murad Husain forwarded corrected pdf copy of C0405 Protocol and the Perez-Ruiz Literature-"Effect of Urate-Lowering Therapy on the Velocity of Size Reduction of Tophi in Chronic Gout" Vol. 47. No 4. August 15, 2002 pp. 356-360, to the FDA-Pratibha
1/25/2006	SPI	Correspondence	**Email:** From Murad Husain to the FDA-Pratibha Rana regarding SPA: Our Response
1/26/2006	SPI	Information Amendment - Pharmacology/ Toxicology	**Submission:** SN064 Information Amendment: Pharmacology/Toxicology SN064. Submission of draft audited reports for studies 7533-100, WIL 441007 and WIL 441008. (Our acknowledgement received on February 2, 2006).
1/27/2006	FDA	Correspondence	**Fax:** From the FDA-Pratibha Rana: FDA letter dated 1/27/06 re: Response to a Request for SPA.
1/31/2006	SPI	Correspondence	**Email:** Murad posed questions to P. Rana: proposal for a Type A meeting to discuss SPA for phase 3 protocol; is it necessary to submit any more phase 2 summary data in support of begininning phase 3?
1/31/2006	SPI	Correspondence	**Submission:** SN065 General Correspondence: Request For A Type Meeting for SPA review of protocol C0405 (Our acknowledgement received on 2/8/06).
2/6/2006	FDA	Correspondence	**Email: From Pratibha Rana-FDA regarding two questions, 1. Receipt of the fax requesting the Type A Meeting, 2. submission of the updated safety information, including all SAE's along with the phase 3 studies.**
2/7/2006	SPI	Correspondence	**Email:** Murad posed question regarding the composition of placebo to be used in the P3 clinical studies.
2/10/2006	FDA	Correspondence	**Email:** P. Rana notified Murad that his question was forwarded to the Product reviewers.
2/14/2006	FDA	Briefing Book	**SN066 Type A Meeting: Information Package**: Submission of revised C0405 protocol based on FDA recommendations in FDA letter dated 1/27/06; submission of RadPharm Charter for C0405 and request for a SPA review meeting for the revised protocol (Our acknowle
2/14/2006	FDA	Correspondence	**Email: From Pratibha Rana-FDA regarding the submission of the Information Meeting Package.**
2/16/2006	SPI	Annual Report	**Serial #067: Annual Report covering periods**: 1/1/05 – 12/31/05. (Our acknowledgement received on 2/21/06).
2/22/2006	SPI	Briefing Book	**Email:** From Murad Husain to FDA - Pratibha Rana forwarding the PDF version of the briefing package as attachments.

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2/22/2006	SPI	Correspondence	**Serial #068: Information Amendment: Clinical** Submission of revised Investigator Brochure, version 5 dated February 15, 2006 (Our acknowledgement received on 3/2/06).
2/28/2006	SPI	Briefing Book	**Email:** From Murad Husain to FDA – Pratibha Rana, forwarding E-copy of the Briefing Package # 2.
2/28/2006	SPI	Briefing Book	**Email:** From Murad Husain to FDA – Pratibha Rana, forwarding E-copy of the Briefing Package # 1.
3/1/2006	SPI	Clinical	**SN069: Information Amendment: Clinical.** Draft version of the Investigator's Brochure, Version 5.0 dated Feb 9 was inadvertently included in SN068, rather than the final version. The final Investigator's Brochure, Version 5.0 dated February 15, 2006 is in
3/1/2006	FDA	Correspondence	**Email:** FDA-Pratibha Rana regarding CMC Question.
3/1/2006	SPI	Correspondence	**Email:** From Murad Husain to FDA – Pratibha Rana, committing to forward 2 CD's of the January 26, 2006 SN064 submission via Fedex to Sara Stradley at the FDA in Silver Spring, MD on 3/2/06.
3/1/2006	FDA	Correspondence	**Email:** FDA-Pratibha Rana regarding CMC Question.
3/13/2006	FDA	Correspondence	**Email:** From Pratibha Rana to Murad Husain re: Clearance of letter.
3/13/2006	SPI	CMC	**Email:** From Murad Husain to FDA-Pratibha Rana re: Proposed TC with Dr. Rappaport.
3/15/2006	SPI	Clinical	**Email:** From Murad Husain to Pratibha Rana regarding email information request for AUC and Cmax data for 8mg dose of PEG-uricase.
3/15/2006	SPI	Correspondence	**Email:** From Murad Husain to FDA-Pratibha Rana re: 54-day study in rats was done, in study number 20-4-0188-00. Final study report was submitted in original IND SN #000.
3/15/2006	FDA	Correspondence	**Email:** From FDA-Pratibha Rana to Murad Husain re: receipt of CD, and question regarding the toxicology study in rats.
3/16/2006	FDA	Clinical	**Fax:** FDA Response- from Pratibha Rana with Response to questions on the 2/14/06 Meeting Package.
3/17/2006	SPI	New Protocol	**SN070: Special Protocol Assessment: Revised Protocol C0405** sent to Robert Rappaport, MD, Director, copy to Robert Meyer, Director, along with Desk Copy to Pratibha Rana. (Our Acknowledgement received on 3/27/06).
3/17/2006	SPI	Correspondence	**Email:** From Murad Husain to FDA-Pratibha Rana, providing Dial-In number and passcode for teleconference at 2pm.
3/20/2006	FDA	Correspondence	**Email:** From FDA-Pratibha Rana to Murad Husain with the information requested by the Pharmacology Toxicology Team needed to conduct proper review of the application.
3/20/2006	SPI	Correspondence	**Email:** From Murad Husain to FDA-Pratibha Rana, that we did formally submit to the revised protocol to the document room.

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3/20/2006	SPI	Correspondence	**Email:** From Murad Husain to FDA-Pratibha Rana the PDF E-Copy of the 3/17/06 SN070 Cover Letter.
3/30/2006	SPI	Correspondence	**Email:** From Murad Husain to FDA-Pratibha Rana. PDF Copy of cover letter for EOP2 Meeting Package was sent.
3/30/2006	FDA	Correspondence	**Email:** From FDA-Pratibha Rana to Murad Husain requesting a PDF copy of the cover letter dated June 21, 2005 containing response to information request.
4/3/2006	SPI	Correspondence	**Email:** From Murad Husain to FDA-Pratibha Rana re: request status of several issues possibly related to review of SPA; inquiry regarding pharm/tox. data and notification of upcoming CMC amendment pending receipt of FDA CMC Advice letter
4/4/2006	FDA	CMC	**Email:** From FDA-Pratibha Rana re: "CMC Advice Letter".
4/5/2006	FDA	CMC	**Fax:** From the FDA-Pratibha Rana "CMC Advice Letter"dated 4/4/06
4/10/2006	FDA	CMC	**SN071: Information Amendment: Chemistry, Manufacturing and Control.:** Submission of process and facilities information in support of the manufacture of the phase 3 clinical material
4/12/2006	SPI	Pharmacology/ Toxicology	**SN072: Response to FDA Request for Information:** Pharmacology/Toxicology. (2 Volumes). Submission of methods validation study reports , TK study reports, and immunogenicity study reports conducted in support of study #7533-100; submission of dosing soluti
4/20/2006	SPI	CMC	**SN073: Information Amendment-Chemistry, Manufacturing and Contro.** The Certificate of Analysis for placebo (lot# 5682003102) to be used in the upcoming Phase 3 clinical trials under Protocols C0405 and C0406 beginning in early May of 2006. (Our acknowle
4/25/2006	FDA	Correspondence	**Email:** From Pratibha Rana to Murad Husain re: SPA Status of PEG-uricase.
4/25/2006	FDA	Correspondence	**Email:** From Murad Husain to Pratibha Rana re: SPA Status of PEG-uricase.
4/27/2006	SPI	CMC	**SN074: Information Amendment-Chemistry Manufacturing and Contrd.** The revised Certificate of Analysis for Puricase (lot # 5682003100) to be used in the upcoming Phase 3 clinical trials under Protocols C0405 beginning in early May of 2006. (Our acknowled
4/28/2006	FDA	Correspondence	**Email:** From FDA Pratibha Rana to Murad Husain re: Summary of SPA Letter due on May 4th.
4/28/2006	SPI	Correspondence	**Email:** From Murad Husain to FDA-Pratibha Rana re: Summary of SPA Letter due on May 4th.
5/3/2006	FDA	Clinical	**Fax:** From the FDA SPA Response Letter.
5/4/2006		New Protocol	**SN075:** Protocol Amendment: New Protocol & Protocol Amendment: New Investigator. Protocol's submitted: Protocol C0405 "Randomized, Multicenter, Double-Blind, Placebo-Controlled Efficacy and Safety Study of 8mg PEG-uricase in Two Dose Regimens in Hyper

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5/5/2006	FDA	New Protocol	**Email:** Foma forwarded to the FDA-Pratibha Rana a copy of the cover letter to the submission of the final protocols (C0405 and C0406) and new investigators, SN 75
5/5/2006	FDA	Clinical	**SN076: General Correspondence**: In reference to the submission of May 4, 2006 SN075, the description of responsibilities for Kendle International Inc., our contract research organization (CRO), was inadvertently omitted. Two attachments, one for Study C04
5/23/2006	SPI	Correspondence	**Email:** From Murad to Pratibha regarding a proposal to meet with the Agency on CMC Development for PEG-uricase.
5/26/2006	SPI	Correspondence	**Email:** Telephone call from Murad to the FDA - Pratibha Rana to follow-up regarding the proposal to meet with the Agency on CMC Development for PEG-uricase.
6/5/2006	SPI	Correspondence	**Email:** From FDA - Pratibha Rana to follow-up with Murad regarding the proposal to meet with the Agency on CMC Development for PEG-uricase.
6/6/2006	SPI	Pharmacology/ Toxicology	**SN077: Information Amendment: Pharmacology/Toxicology**. Final Study Reports for WIL-41007 and WIL-41008 submitted. (Our acknowledgement received on 6/15/06).
6/9/2006	FDA	Clinical	**Email:** From FDA Pratibha Rana. The Review Team agrees with the company that he could be enrolled in their Phase-3 PEG-uricase trial.
6/20/2006	SPI	New Investigator	**SN078: Protocol Amendment: New Investigator**. We are amending the IND to include additional study sites for Protocol's C0405 (sites) and C0406 (sites). (Our acknowledgement received on June 26, 2006).
7/12/2006	SPI	Correspondence	**Email:** From Murad Husain to FDA-Pratibha Rana regarding proposal to amend Protocol's C0405 and C0407
7/13/2006	SPI	Protocol Amendments	**SN079: General Correspondence: Proposal to Amend Protocols**. We are proposing to amend protocols C0405 and C0406 (SPA) to allow participation of patients with inter-flare intervals less than a week to participate in the PEG-uricase Phase 3 program. (Our a
7/19/2006	SPI	New Investigator	**SN080: Protocol Amendment: New Investigators** and Sites: C0405: K. Hackshaw, J. Lisse, J. Sundy; C0406: A. Dillon, G. Gottschlich, D. Lalter, K. Kolba, L. Moreland, K. Oelke, S. Wolfe. We are amending the IND to include additional study sites for Protoc
7/22/2006	SPI	Briefing Book	**Fax:** Dr. James Reese, PhD forwarded his 1st draft of questions/comments prior to the EOP 2 meeting on July 26, 2005. 7/22/05
7/24/2006	FDA	Correspondence	**Email:** From Pratibha Rana to Murad Husain to make a formal submission to obtain the FDA's advise on two more minor modifications in our clinical program.
7/25/2006	FDA	Correspondence	**Email:** From Murad to the FDA-Pratibha Rana regarding changes to the protocol and what Regulatory Procedure we should follow.

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8/1/2006	FDA	Correspondence	**Email:** From Murad Husain and the FDA Sara Stradley regarding protocol Amendments. Per Sara Stradley, the amendments will need to be reviewed before commenting.
8/7/2006	SPI	Protocol Amendments	**SN081: General Correspondence: Proposal to Amend Protocols** C0405 & C0406 by removing the previously specified Open Label Extension dose Regimen, which will be determined upon enrollment into that study.
8/10/2006	SPI	Protocol Amendments	**SN082: Protocol Amendment: New Investigator.** We are amending our IND to include additional study sites for Protocol's C0405 and C0406.
8/18/2006	SPI	CMC	**SN083:** General Correspondence: Request for Type B CMC-Specific Meeting to discuss Puricase® (polyethylene glycol [PEG]-uricase) chemistry, manufacturing and controls related developmental issues (Ref. E-mail message from Ms. Pratibha Rana, dated June 9,
8/18/2006	FDA	Correspondence	**Email:** From FDA-Sara Stradley-Response to Request for Type B CMC-Specific Meeting. The FDA is scheduling meetings for late December.
8/18/2006	SPI	Correspondence	**Email:** From Murad Husain to the FDA – Sara Stradley regarding Request for Type B CMC-Specific Meeting.
8/28/2006	SPI	Correspondence	**Email:** From Murad Husain to the FDA-Sara Stradley following up on request for a Type B CMC Meeting for PEG-uricase.
8/30/2006	SPI	Correspondence	**Email:** From Murad Husain to FDA-Sara Stradley in response to Murad's email on August 30, 2006. The pre-meeting briefing package will be submitted 4 weeks prior to the meeting date. Murad has requested if Sara receives the meeting date earlier than expe
8/30/2006	FDA	Correspondence	**Email:** From FDA-Sara Stradley in response to Murad's follow-up email request for a Type B CMC Meeting for PEG-uricase on August 28, 2006. Sara Stradley would like to know when she can expect meeting package along with the 10 desk copies.
9/1/2006	FDA	Correspondence	**Letter:** From the FDA confirming the date and location of the CMC-Specific Meeting Type B.
9/1/2006	FDA	Correspondence	**Email:** From FDA-Sara Stradley in response to Murad's email on August 30, 2006 request for the meeting date. Sara has informed Murad that she has scheduled the meeting date on November 21, 2006 from 2-3pm, which will be held at the NIH Campus. Sara has
9/20/2006	FDA	Clinical	**Letter:** FDA response to proposed revisions to C0405 and C0406 protocols. FDA agreed to a protocol revision allowing inclusion of patients that experience gout flares that are not resolved for at least 1 week prior to the first study drug treatment, if t
9/22/2006	SPI	New Investigator	**SN084:** Protocol Amendment: New Investigator. We are amending our IND to include the following additional study sites for Protocol's C0405 & C0406.
10/13/2006	SPI	Clinical	**SN085: General Correspondence – Briefing Package** for CMC/Type B on November 21, 2006

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10/19/2006	SPI	Clinical	**SN086: General Correspondence- Request for waiver for IRB** for study sites in Canada (C0405) and Mexico (C0406). Also request release from obligation to send copies of IRB approvals and approved I/C forms.
10/31/2006	SPI	New Investigator	**SN087: Protocol Amendment: New Investigator.** Addition of PIs to C0405 and C0406; and submit revised FDA 1572 forms--- C0405- Nussbaum (new), Klein, Lisse; C0406 – Gorevic (new), Gottschlich.
11/9/2006	SPI	New Investigator	**SN 088: Protocol Amendment: New Investigator-** Addition of 4 sites in Mexico to C0405 and 4 sites in Canada to C0406.
11/16/2006	SPI	New Protocol	**SN089: Protocol Amendment: New Protocol/** Change in Protocol – Submission of C0407 protocol; submission of Amendment # 2 to C0405 and C0406.
11/20/2006	FDA	Correspondence	**E-mail:** From Pratibha Rana to Murad Husain concerning the Division's response to the questions from CMC meeting package for November 21, 2006 meeting (SN085).
11/30/2006	FDA	New Investigator	**SN 090: Protocol Amendment: New Investigator**—Addition of PIs to C0405 and C0406. Michet added to C0405; Yazici added to C0406.
12/1/2006	SPI	Meeting Minutes	**SN 091: General Correspondence**: Type B CMC Meeting Minutes Held on 11/21/06 (Savient authored minutes)
12/4/2006	SPI	Correspondence	**Email:** From Murad to Pratibha concerning Parinda Jani missing from meeting attendee list held 11/21/06.
12/13/2006	SPI	IND Safety Reports	**SN 092: IND Safety Report- Initial Report**: Mfr. # 06US000052; patient # 101-005. Report of hospitalization due to pancreatitis. Becker's site.
12/21/2006	FDA	Meeting Minutes	**Email containing FDA letter dated 12/21/06:** From Pratibha Rana to Murad Husain concerning the Type B CMC Meeting held 11/21/06 between SPI and the FDA. FDA Meeting Minutes are attached to the e mail.
12/22/2006	SPI	New Investigator	**SN 093: Protocol Amendment: New Investigator /** Information Amendment: Clinical: Submit Fiechtner to C0407 study; submit revised 1572 forms for Codding (405); Oelke (406); and Yazici (406).
1/2/2007	SPI	Correspondence	**Email:** Follow up from Murad Husain to Pratibha Rana concerning "Request for an IRB Waiver for Foreign Study Sites".
1/24/2007	SPI	New Investigator	**SN 094: Protocol Amendment: New Investigator /** Information Amendment to include 3 additional study sites for Protocol C0405 and three PI's who will be conducting the C0407 Protocol.
2/21/2007	SPI	Annual Report	**SN 095:** Annual Report covering the period 1/1/2006 – 12/31/2006.
2/22/2007	FDA	Clinical	**Letter:** From Bob Rappaport to Murad Husain confirming the IRB Waiver has been granted in response to the letter request dated 10/19/06 from SPI.
2/22/2007	SPI	New Investigator	**SN 096: Protocol Amendment: New Investigator-** Addition of four sites to the C0407 protocol (Dillon, Gonter, Gottschlich, Riordan)
2/23/2007	SPI	IND Safety Reports	**SN 097: IND Safety Report-** Follow-up Report: Mfr # 06US000052; patient # 101-005.
3/19/2007	SPI	New Investigator	**SN098: Protocol Amendment: New Investigator /** Information Amendment – Information Amendment to include documentation for eight Principal Investigators who will be conducting the C0407 Protocol. Addition of 8 sites to C0407 (Baraf, Bookbinder, Butler, Fun
3/21/2007	SPI	Protocol Amendments	**SN099: General Correspondence: Proposal to Amend Protocols** C0405 and C0406.SPI would like to request comments and concurrence with the proposed revisions fom the FDA.
3/22/2007	SPI	Clinical	**SN100: Information Amendment: Clinical**– SPI amended IND:10122 to include a revised Investigator's Brochure, v 6.0 dated 3/16/07.

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3/29/2007	SPI	CMC	**E mail**: From Murad Husain to Pratibha Rana--question regarding whether or not accelerated stability data will be required for the BLA submission.
4/2/2007	FDA	CMC	**E mail**: From Lisa Basham to Murad Husain—Has forwarded SPI inquiry to product reviewer. Asked Murad to check back next week if no response by then.
4/16/2007	FDA	CMC	**Email:** From Lisa Basham- response to Murad's follow-up email originally sent to Pratibha Rana dated March 29, 2007, concerning a question SPI had proposed to submit drug product stability data from both accelerated and real-time conditions in the BLA
4/20/2007	SPI	New Investigator	**SN # 101 – Protocol Amendment – New Investigator**- Add 2 PIs to C0407 (Fraser and Thurmond-Anderle)
5/9/2007	FDA	New Investigator	**SN # 102 – Protocol Amendment – New Investigator** –Add 6 PI's to CO407(Barkhuizen, Torres, Codding, Mandel, Huff, D'Ambrosio) and submit 1 revised 1572 form for C0405 (Yood).
5/17/2007	SPI	New Investigator	**SN # 103 – Protocol Amendment: New Investigator-** Add 9 PIs to C0407 (Becker, Hackshaw, Kerr, Lisse, Nussbaum, Oelke, Oza, Raja, Sundy) and submit 2 revised 1572 forms for C0406 (Dillon, Torres).
5/17/2007	SPI	Clinical	**Email:** from Foma Rashkovsky request for written concurrence from FDA regarding implementation of changes to the C0405 and C0406 protocols due to the current hydrocortisone shortage
5/22/2007	FDA	Clinical	**Email:** From Lisa Basham to Foma Rashkovsky: re: Phase 3 studies and shortage of hydrocortisone. SPI request not to substitute long-acting corticosteroid for hydrocortisone. FDA suggested submission to IND.
5/25/2007	FDA	Clinical	**Email:** FDA suggesting we submit a protocol change to the IND for their review and they will respond.
5/30/2007	SPI	Clinical	**SN 104: Information Amendment – Clinical**– Reports on Plasma Uric and Serum Uric Samples and use of a proposed correction factor in Protocol C0405 and C0406.
6/1/2007	SPI	Protocol Amendments	**SN 105: Change in Protocol** Amendment 3 for C0405 and C0406 Amendment provides guidance for using alternative corticosteroids when the hydrocortisone shortage necessitates a substitution.
6/14/2007	SPI	Protocol Amendments	**E-Mail:** Request from Murad Husain to Lisa Basham at FDA: 1. Status update of Amendment 3 to C0405 and C0406 SN 099 2. Request for Type B Meeting in July or August - re: Clarification on SAP submission to the BLA
6/18/2007	SPI	Clinical/CMC	**SN 106: Protocol Amendment: New Investigator:** Add New Investigators to C0407: Steven Klein, MD, Randal Earl White, MD, Robert A. Yood, MD. Revised 1572 for: Alan Kivitz, MD (C0406) add SI (Smith). **Information Amendment** Chemistry/Microbioology: New cont
6/20/2007	SPI	Clinical	**Telephone Contact Report**: Murad called Lisa Basham today, 6/20/07, as a follow-up to our e-mail message from June 14 proposing for a Type B meeting to present and agree on clinical data format for our upcoming BLA, and to enquire about the status of our p
6/20/2007	SPI	Protocol Amendments	**SN 107: Protocol Amendment** – Change in Protocol: C0407 Amendment 1 - This amendment contains the provisions of draft Amendment # 3 to C0405/6, submitted as SN099. Amendment provides for increased enrollment time window between 405/6 and 407; requirement f
7/6/2007	SPI	Clinical	**SN 108: Protocol Amendment – Change in Protocol** C0407 Amendment 1 - This amendment contains the provisions of draft Amendment # 3 to C0405/6, submitted as SN099. Amendment provides for increased enrollment time window between 405/6 and 407; requirement f
7/12/2007	SPI	Clinical	**SN 109: Protocol Amendment – Change in Protocol**: Amendment 4 to C0405 and C0406 which includes revisions submitted as Amendment #3 in SN 105 on June 1, 2007.

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7/19/2007	SPI	Clinical	**SN 110: Information Amendment and General Correspondence** – Submitted SAP for review and concurrence for C0405, Request for Type C Meeting to reach agreement on proposed SAP and specific clinical data in the BLA, and questions.
7/23/2007	SPI	Clinical/CMC	**SN 111 – Information Amendment: Chemistry/Microbiology and Clinical – Protocol Amendment: New Investigator:** New PI for C0407 Janet Pope, MD, Revised FDA 1572 A. Kavanaugh, MD to include additional subinvestigator, Hennigan, COA for Lot 7088, COA for lot
8/1/2007	SPI	Protocol Amendments	**E-mail** from Murad Husain to Lisa Basham on August 1, 2007 and August 2, 2007 for follow-up on SN 104, Info Amendment: Clinical; SN 105 – Protocol Amend – Change in Protocol – Amend #3 ; SN 109 Protocol Amend – Change in Protocol – Amend #4 to Phase III; S
8/2/2007	FDA	Protocol Amendments	**E-mail** from Lisa Basham: Meeting request was denied by FDA will respond in writing; FDA is waiting for a response from their Stat Team leader on projected timeframe on the SAP and will notify us as soon as they have the information.
8/3/2007	SPI	Clinical	**SN 112 – Information Amendment – Clinical**: Amended IND to include six bioanalytical assay validation. In addition to FDA recommended antibody assays, we have validated an "Enzyme Linked Immunosorbent Assay (ELISA) for the Detection of Anti-Uricase IgG an
8/17/2007	SPI	New Investigator	**SN 113 – Protocol Amendment: New Investigator:** Added Daryl K. MacCarter, MD, PI, to C0407. Amended Andre Barkhuizen, MD, PI, to 0406 for change of address
9/13/2007	FDA	Protocol Amendments	**E-Mail** from Lisa Basham dated 9/13/07 re: follow- up on 4 submission: SN 104, Info Amendment: Clinical; SN 105 – Protocol Amend – Change in Protocol – Amend #3 ; SN 109 Protocol Amend – Change in Protocol – Amend #4 to Phase III; SN 110 Info Amend – Clini
10/1/2007	FDA	Protocol Amendments	**Email** from Lisa Basham dated 8/2/07 status of 4 submissions: Items 1-3 is circulating; waiting for final response to Item 1 and the pkg (item 4) but expect to have them within the next week or so. Send meeting request for CMC meeting.
10/1/2007	SPI	Protocol Amendments	**Email** to Lisa Basham dated 10/1/07on status of 4 submissions: SN 104, Info Amendment: Clinical; SN 105 – Protocol Amend – Change in Protocol – Amend #3 ; SN 109 Protocol Amend – Change in Protocol – Amend #4 to Phase III; SN 110 Info Amend – Clinical Sta
10/2/2007	SPI	Correspondence	**SN 115 - General Correspondence - Request for Review of a Proposed Proprietary Name**: Submitted Tophuric and Puricase®. Included Summary of Draft Labeling, Rationale for Choice of Proposed Proprietary Name(s), Executive Summary of Development Program, USA
10/2/2007	SPI	New Investigator	**SN 114 – Protocol Amendment – New Investigators**: Submitted to C0407: John L. Harshbarger, MD, Brian F. Mandell, MD, PhD, Craig Scoville, MD, PhD, Edward T. Treadwell, MD
10/3/2007	SPI	Correspondence	**Email from Murad to Lisa Basham** requesting amount of time before a decision is made on the proposed name(s).
10/3/2007	FDA	Correspondence	**Email from Lisa Basham on October 3, 2007** informing SPI it takes approx 180 days, plus a week or so, for a determination of the proposed name.
10/4/2007	FDA	Change in Protocol	**Email** with FDA Advice Letter on SN 105 and 109 RE: C0405 and C0406 Protocol Changes
10/4/2007	FDA	Clinical	**FDA letter**- regarding response to SN 105 and 109 containing protocol amendments for C0405 and C0406
10/8/2007	SPI	Change in Protocol	**SN 116 – GC** – Response to FDA's letter of 10-4-07 regarding C0405 and C0406 protocol amendments 3 and 4 submitted as SN105 and 109 on June 1 and July 12, 2007, respectively
10/11/2007	FDA	Correspondence	**FDA Letter dated 10/4/07** hard copy - regarding Amendments Submitted June 1 and July 12, 2007 for C0405 and C0406

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10/11/2007	FDA	Correspondence	**E-mail from Lisa Basham** advising Murad Husain of contact person to establish email encryption between FDA and SPI.
10/11/2007	SPI	New Investigator	**SN 117** – New Investigators for C0407 – Mexico: Ruben Burgos-Vargas, MD Sergio Ramon Gutierrez-Urena, MD Nora Janitzia Vazquez-Mellado Cervantes
10/12/2007	SPI	Pharmacology/ Toxicology	**SN 118:** Final Study # 7533-100 - 39-Week Repeated Intravenous Injection Chronic Toxicity and Toxicokinetic Study with Puricase® in Dogs with a 12-week recovery
10/12/2007	SPI	Correspondence	**Email:** Ken Royer, from IT, contacted Wendy Lee at FDA for assistance and details involved with email encryption set up between FDA and SPI.
10/15/2007	FDA	Clinical	**Email** with requested document attached; sent in response to FDA email request dated 10/15/07 for a copy of SN 104 containing analytical method being used in assaying plasma uric acid in Phase 3
10/19/2007	FDA	Correspondence	**Email** from FDA to Ken Royer re: Encryption Process with attachment of detailed software/equipment for encryption set-up between FDA and SPI
10/24/2007	FDA	Correspondence	**Email** from FDA's Wendy Lee to Ken Royer, IT, follow-up on encryption procedure between Savient and FDA
11/6/2007	FDA	Clinical	**Email** from Lisa Basham re: FDA has accepted Savient proposals in SAP submitted in SN110,there is one outstanding question regarding CDISC STDM
11/7/2007	SPI	Protocol Amendments	**SN 119 – Protocol Amendment** – New Investigators: C0407 Clement Michet; revised FDA 1572 forms for C0406 Kurt Oelke and Arnaldo Torres; C0405 John Huff, Clement Michet, Jr., Michael Yood, MD
11/16/2007	FDA	Clinical	**Email** from Lisa Basham re: response to request for update regarding pending issues: Uric Acid Test Method and SAP. May know by next week, 11/19-23/07
11/21/2007	SPI	CMC	**SN 120** – CMC update: Update to the manufacturing information for mPEG-NPC; and notification of a change in the contract filler
11/30/2007	SPI	Protocol Amendments	**SN 121** – Protocol Amendment – New Investigator for C0407 – Mexico - Hilario Ávila Armengol, MD
12/5/2007	FDA	Correspondence	**Email** – FDA's response to when a Type B meeting can be scheduled – April 2008 is the earliest.
12/12/2007	FDA	Correspondence	**Email** – Request to Lisa Basham for Fax Number to send Dr; Rappaport Confidential Information
12/13/2007	SPI	Clinical	**SN 122** – Preview of Phase 3 top line efficacy and safety results prior to issuance of press release
12/14/2007	SPI	CMC	**SN 123** – Request for Type B Pre-BLA Meeting to discuss content and format of the BLA
1/10/2008	FDA	Correspondence	**Email** from L. Basham-Pre-BLA Meeting is scheduled for April 17, 2008
1/10/2008	SPI	Protocol Amendments	**SN 124** – Submitted Amendment 2 to C0407 and 4 revised 1572;s: 2 for C0405 Michet and Sundy, and 2 for C0407 Barkhuizen and Lisse
1/29/2008	FDA	Clinical	**FDA** letter dated 1/29/08 attached to 1-30-08 L. Basham e mail: FDA response to SN110- 7/19/07 Request for Type C Mtg to discuss SAP
1/30/2008	FDA	Clinical	**Email** from Lisa Basham with attached FDA Letter in response to SN110 dated 7/19/07 Request for Type C Mtg to discuss SAP
1/31/2008	FDA	Correspondence	**Email** from L. Basham requesting our dialogue with CMC Reviewers, at NIH Campus to go through Lisa Basham.

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Date	From	Info Type	Description
2/22/2008	SPI	Annual Report	**SN 126** – 2007 Annual Report
2/22/2008	SPI	Protocol Amendments	**SN 125** – Submitted Protocol C0409 and Revised 1572 for Norman Gaylis
3/13/2008	SPI	Briefing Book	**Email** from L. Basham on status, copies, and delivery of Briefing Book.
3/17/2008	SPI	Briefing Book	**SN 127** – Briefing book outlining questions for April 17, 2008 FDa Meeting
3/17/2008	SPI	Correspondence	**Email to FDA** testing Encrypted Message capability
3/20/2008	SPI	Briefing Book	**Email** from L. Basham requesting 14 additional copies of pre-BLA meeting BB and from M. Husain inquiring if BB is adequate background for the meeting
4/3/2008	SPI	Protocol Amendments - New Investigator	**SN 128** – New Investigators for C0409 Drs. Baraf and Barkhuizen. Revised 1572 for Barry Getzoff for C0407
4/3/2008	SPI	Briefing Book	**Email** response from FDA regarding setting up encrypted messaging to enable safe e-transmission of supportive clinical pharmacology data for pre-BLA meeting package
4/4/2008	SPI	Other - Addendum to Briefing Book	**SN 129 – GC** – Addendum to Pre-BLA Meeting Package submitted on 3/17/08 per FDA request: Clinical Pharmacology Data Sets
4/7/2008	SPI	Briefing Book	**Email** to Lisa Basham with PDF SN 129 attached Addendum to Briefing Package with Clinical Pharmacology data.
4/10/2008	SPI	Briefing Book	**Email** to L. Basham follow-up to request for Agency answers to Pre-BLA questions and request to include an additional CMC question.
4/15/2008	FDA	Briefing Book	**FDA letter** dated 4/15/08 -Attached to 4/15/08 Email from L. Basham RE: Agency responses to 4/17/08 Pre-BLA Meeting Questions
4/15/2008	FDA	Briefing Book	**Email** from L. Basham with attached 4/15/08 FDA Letter containing Responses to Pre-BLA Meeting Questions
4/22/2008	FDA	Correspondence	**Email** from L. Basham responding to Savient email requesting a status update on the FDA review of proposed proprietary name- still checking
4/25/2008	FDA	Correspondence	**Email** from L. Basham correcting Attendee List for Pre-BLA Meeting to reflect actual attendees
4/25/2008	FDA	Correspondence	**Email** from L. Basham confirming CMC Questions to be discussed at the scheduled pre-BLA meeting and confirming final Savient Attendee List
4/30/2008	FDA	Correspondence	**Email** from L. Basham with informal FDA response to Savient proprietary name request – Tophuric deemed acceptable
4/30/2008	SPI	Information Amendment - Clinical	**SN 130** Submit revised 1572 forms for C0407 Investigators; Dillon, Fiechtner, Gottschlich, Oza, Raja, Yood and submit RadPham Charters to be used with C0407 and C0409
5/12/2008	SPI	General Correspondence - Meeting Minutes	**SN 131** – Savient Minutes from 4-17-08 Pre-BLA Meeting
5/13/2008	FDA	Correspondence	**FDA Letter** – FDA Response (No Objection at this time) to Savient Request for Review of proposed proprietary name -Tophuric
5/14/2008	FDA	Correspondence	**Email** from L. Basham assigning Submission Tracking Number 125293/0/0 for the BLA
5/19/2008	FDA	Meeting Minutes	**Email** from L. Basham with attached FDA version of 4-17-08 Pre-BLA Meeting Minutes. FDA letter dated 5-16-08.

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5/22/2008	SPI	General Correspondence - Meeting Minutes	SN 132 – General Correspondence - Savient Pharmaceuticals, Inc.comments on FDA version of 4-17-08 Pre-BLA Meeting Minutes
6/9/2008	SPI	Protocol Amendment - New Investigator	SN 133 - Protocol Amendment - New Investigator - Added John Sundy to PI for C0409
6/12/2008	FDA	Meeting Minutes Comments	**Email** Request from Murad for comments on meeting minutes sent in SN 132. Lisa heard nothing from the chemists on item 3. Unofficially, the clinical team gave okay for revision 1 and 2
7/9/2008	FDA	Email	**Email** from L. Basham confirming CMC and Clinical points of Meeting Minutes are acceptable. Submission date moved to Mid-October due to Alternate Mfg Site
7/9/2008	SPI	Protocol Amendment and Information Amendment	SN 134 – Protocol Amendment – New Investigator for C0409 Saima Chohan, MD, with CV, IRB Approval and and Informed Consent Form. Revised 1572 for C0407 for Dillon, Huff, and Oza, Information Amendment - Investigator's Brochure, Version 7.0
8/12/2008	FDA	Email	**Email** from L. Basham to send Safety updates on day 120. Minutes have not been issued yet.
8/27/2008	SPI	Information Amendment - Clinical	SN 135 - Information Amendment - Revised RadPharm Independent Review Charter Version 3
8/27/2008	FDA	Email	**Email** from L. Basham - Trying again to get feedback on the comparability protocol. Will try to get minutes this week
9/4/2008	FDA	Email	**Email** from L. Bahsam - Response to alternate manufacturing site
9/10/2008	FDA	Email	**Email** from L. Basham - Discrepancy in what happens when patients discontinue use of drug
9/22/2008	SPI	Submission	SN 136 - Protocol and Information Amendment - Clinical - Add new PI to take over for Daryl MacCarter(Collins) and change site address.
9/22/2008	FDA	Email	**9-22-08 - Email** from L. Basham with Pre-BLA Meeting Minutes Final Attached
9/29/2008	FDA	Email	**9/29/08 FDA Email** - What is your ETA for PEG BLA - End of October
10/6/2008	FDA	Email	**Email** from L. Basham - re: Cardiovascular Events. Request to submit an accounting and safety analysis of all deaths reported with the product along with a safety assessment of all serious cardiovascular thromboembolic adverse events. Include all serious
10/7/2008	SPI	Email	**Email** from M. Husain re: CV Events. Response to FDA Request for information re: CV Events
10/15/2008	FDA	Email	**Email** from L. Basham re: Review of Proprietary Name w/BLA and CV Events Teleconference
10/15/2008	FDA	Email	**Email** from L. Basham re: PPI, REMS, submission of Proprietary Name, DP and DS Info
10/24/2008	FDA	Email	**Email** from L. Basham re 3 Questions - Data submitted to FDA no later than 3 months into review period.
11/4/2008	SPI	Information Amendment - Clinical	SN 137 - Submitted revised 1572s for Butler, Gaylis, Lisse, Mandel and Yood for C0407
1/19/2009	SPI	Information Amendment - Clinical	SN 138 - Submitted revised 1572's for Drs. Baraf, Gottschlich, Leonard(replaced Riordan), Wolfe for C0407
1/28/2009	SPI	Safety Report	SN 139 - Submitted Initial Report for Patient # C0406/325-001 from C0407-AE: Necrotizing Skin Lesions on Face and Hands (Dermatitis). Mfr Report # 09US000316.

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Date	From	Info Type	Description
2/12/2009	SPI	Safety Report	SN 140 - Submitted Follow-up report for Patient # C0406/325-001 from C0407- AE: Necrotizing Skin Lesions on Face and Hands (Dermatitis). Mfr Report # 09US000316.
2/23/2009	SPI	Annual Report	SN 141 - Annual Report covering period 1/1/08 to 12/31/08
2/27/2009	SPI	Info Amend - Clinical	SN 142 - Revised 1572 for Protocol C0407 for Baraf, Lisse, Nussbaum, Scoville and C0409 Baraf
3/20/2009	SPI	Safety Report	SN 143 - Submitted Follow-up Report for Patient #C0406/325-001 from C0407 - AE: Necrotizing Skin Lesions on Face and Hands
3/27/2009	SPI	Info Amend - Clinical	SN 144 - Submitted Amendment 3 to C0407 protocol extending treatment duration beyond 24 months
6/3/2009	SPI	Info Amend - Clinical	SN 145 - Submitted Revised 1572's for 22 C0407 PI's added 2 new laboratories: Synarc SAS in Lyon, France; and Charles River Labs Preclinical Services Montreal Inc. in Senneville, Quebec, Canada. Three revised DA 1572's include revisions to the Study Site
7/2/2009	SPI	Info Amend - Clinical	SN 146 - Submitted 2 additional labs to be used in the C0407 Study on Revised 1572's and updated addition and deletion of Subinvestigators: Becker, D'Ambrosio, Fraser, Fung, Getzoff, Hackshaw, Harshbarger, Huff, Kerr, Lisse, Mandel, Michet, Raja, Sundy, T
10/28/2009	SPI	Protocol Amendments	SN 147 - **Protocol Amendment: Investigators' Data:** Submitted 30 updated 1572s for Study C0407 (Baraf, Barkhuizen, Becker, Bookbinder, Butler, Collins, A'Ambrosio, Dillon, Fung, Fung, Gaylis Getzoff, Gonter, Gottschlich, Hackshaw, Harsbarger, Hill, Holt, Hu
12/16/2009	SPI	Protocol Amendments	SN 148 - **Protocol Amendment: Investigators' Data:** Submitted 6 updated 1572s for Study c0407 (Barkhuizen, Fraser, Scoville, Sundy, torres, White) addition of Princeton RadPharm lab.
3/17/2010	SPI	Annual Report	**SN149 Annual Report** - reporting period 1/1/09-12/31/09
3/29/2010	SPI	Info Amend - Pharmacology/ Toxicology	**SN 150 Information Amendment: Phamacology/Toxicology:** submitted final reports for WIL 441015, 441016 and 441017.

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10/6/2006	FDA	Administrative	FDA's Official Minutes of Type A Meeting held on September 14, 2009. Purpose of mtg was to discuss deficiences contained in CRL dtd 7/31/09.
10/12/2006	SPI	Administrative	Letter - Disposition of Drug Product Batches, ltr confirming FDA request that peg drug product batches for post-approval commercial purpose using Process B are rejected
10/31/2008	SPI	Administrative	Informing L. Basham BLA has been submitted and attaching a copy of the receipt for transmission
10/31/2008	SPI	Administrative	Letter to Office of Regional Operations in Rockville, MD certifying Savient's Electronic Signature on all correspondence as legally binding
10/31/2008	SPI	Administrative	Letter notifying NJ District Office that BLA was submitted 10/31/08
10/31/2008	SPI	Proprietary Name	**Submission 0000** - Initial Biologic Licenisng Application (BLA) Submission for TRADNAME (pegloticase)...
11/3/2008	FDA	Administrative	L. Basham informing Savient that Diana Walker is the new PM for BLA 125293.
11/5/2008	SPI	PAI	Email to Mary Farbman regarding FDA request to perform PAI at BTG in January and not March and informing FDAthat BTG could be schedule a pegloticase batch process for weeks of January 18 or 25th.
11/5/2008	FDA	PAI	Email from M. Farbman thanking M. Husain for info
11/5/2008	SPI	PAI	Email from M. Husain informing M. Farbman that it takes a month of manufacture a batch of pegloticase and asking for the FDA dates so we can arrange for this batch to be made.
11/5/2008	FDA	PAI	Mary E. Farbman responding to Savient's 11/5/08 email regarding PAI at BTG informing us they will let us know the date of inspection for BTG
11/10/2008	FDA	Proprietary Name	Diana L. Walker, new FDA PM, requesting a tradename review submission and submitting as a separate submission to BLA. Also requesting Savient to include everything submitted in prior tradename submissions etc...
11/10/2008	SPI	Proprietary Name	Email from M. Husain responding to 11-10-08 email from FDA regarding tradename review.
11/10/2008	FDA	Proprietary Name	Response to tradename review request acknowledging request and asking about the timeline of this review...
11/12/2008	FDA	Acknowledgement	FDA letter acknowledging receipt of BLA Submission 0000
11/13/2008	FDA	Acknowledgement	Diane Walker/FDA sending copy of acknowledgement letter for BLA - Submission 0000
11/14/2008	SPI	Proprietary Name	**Submission 0001** - proposing KRYSTEXXA as proprietary name for pegloticase. Re: is made to FDA's 5/13/08 ltr indicating no objections to Tophuric as proprietary name, and Savient now informing that Tophuric is second preference.
11/17/2008	SPI	PAI	Providing information for dial in numbers for 1:30 p.m. TC and attaching formal letter to email describing mfg. schedule to best accommodate FDA plan for PAI
11/18/2008	SPI	PAI	Mary Farbman/FDA re: PAI - providing revised mfg. schedule at BTG based on 11/17 discussion, including hotel accommodation info provided by BTG.
11/19/2008	SPI	PAI	FDA email sending revised scheduled re PAI at BTG in February...
11/20/2008	FDA	ACC	Nicole Vesely introducing herself and advising Savient of upcoming publication of AAC Meeting with a "Letter to Sponsor" attached
11/20/2008	FDA	ACC	Nicole Vesely, PharmD, Designated Federal Official, AAC, advising Savient of tentatively scheduled 3/5/09 AAC mtg., documents needed and providing format requirements of documentation, etc.

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11/21/2008	FDA	ACC	Diane Walker informed Savient our drug classification is new molecular entity (NME) and addressed type of general presentation that was required at AAC mtg...
11/21/2008	SPI	Info Request/CMC	Sent FDA proposal with revised mfg. schedule and requesting M. Farbman's address.
11/21/2008	SPI	Info Request/CMC	Brief summary of 11/17/08 Teleconference regarding revised Manufacturing schedule for proprosed PAI at BTG in Israel
12/1/2008	FDA	Info Request/CMC	Email dated 12/1/08 confirming FDA PAI at BTG 1/28/08 to 2/5/08
12/4/2008	FDA	Administrative	FDA requesting number of attendees at AAC meeting
12/5/2008	SPI	Proprietary Name	**Submission-0002** Amendment to Proprietary Name Review requesting we replace proprietary name, requesting to replace previously submitted and acccepted second choice name Tphuric with Exercase.
12/9/2008	SPI	Amendment/CMC	**Submission 0003** - Letter to FDA Confirmation of Mfg Schedule for PAI with BTG in 2009
12/10/2008	FDA	Acknowledgement	Diana Walker of FDA acknowledging receipt of Submissions 0002 and 0003
12/11/2008	SPI	ACC	Sent FDA List of Consultants for AAC Mtg tentatively scheduled for 3/5/09
12/16/2008	FDA	Info Request/Clinical	FDA requesting Savient submit by 12/22/08 1. assay validation reports for all immunogenicity assays; 2. SOPs for each immunogenicity assay; and 3. relevant supporting assay development data used to establish routine operation parameters of the assay but
12/16/2008	FDA	PAI	FDA requesting PAI Documents to be on site and requesting hotel reservation information for upcoming PAI in 2009.
12/16/2008	FDA	PAI	Document list attached to FDA12/16/08 email requesting that these docs are available for PAI.
12/18/2008	FDA	Info Request/Clinical	S Leibenhaut of FDA Office of Compliance with three questions regarding PUA Data/Timepoints. (See email response to queries on 12/22/08)
12/18/2008	FDA	Info Request/Clinical	Diana Walker, FDA- Statistical review team request subgroup analyses by race, of the effcacy data for studies 405 and 406...
12/18/2008	FDA	Labeling	FDA requesting clarification regarding peel off label on Container and Carton Labeling
12/18/2008	SPI	Labeling	Savient responding to 12/18/08 email regarding peel off label noting that it goes onto patient chart and not iv bag.
12/18/2008	FDA	Labeling	FDA thanking Savient for the quick response to their 12/18/08 info request regarding peel off label on container and carton Labeling. (Email chain begins with email dtd 12/18/08 on line 87.)
12/18/2008	FDA	Info Request/Clinical	FDA Clinical Pharmacology review team requesting the full PK-PD Report for C0403.pdf (See email chain dtd 1/5/09)
12/19/2008	FDA	ACC	FDA requesting status of individuals on the list of consultants and investigators forwarded to them in 12/11/08 email that did not indicate if they are or were former SGE/ACC members.
12/22/2008	SPI	Info Request/Clinical	Response to FDA (Dr. Leibenhaut) queries from 12/18/08 telephone call re: plasma uric acid level assays by CRL and their location, location of the clinical monitoring reports, and data time points for months 3 and 6.
12/22/2008	SPI	PAI	Response to FDA with ground transportation info for PAI in Tel Aviv at BTG for 1/26/09 to 2/5/09
12/22/2008	SPI	PAI	Email sending Itineraries to FDA for PAI Hotel Confirmations for Anderson, Farbman, Chi (Confirmed itineraries attached to email)
12/22/2008	SPI	Info Request/Clinical	**Email submission of 0004** to FDA (Diane Walker) including cover letter and all supporting documents per 12/16/08 request for validationa assays, sops and relevant supporting data.

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12/22/2008	SPI	Amendment/Clinical	**Submission 0004** - Response to 12/16/08 FDA request for assay validation reports for all immunogenicity assays, SOPs for immunogenicity assay and and relevant supporting assay development data.
12/23/2008	SPI	Administrative	Sent FDA w/list of consultants w/wo SGE Status
12/23/2008	SPI	Amendment/Clinical	Sent FDA corrected copy of cover letter for Submission 0004 - Bioanalytical Information Request because pages 12, 13, 14 of the cover ltr, including the summary tables were not included in email submission.
12/29/2008	FDA	General Correspondence	FDA Email forwarding a copy of the FDA's letter accepting the BLA appplication for filing
12/29/2008	SPI	Info Request/Clinical	Email from M. Husain with 9 attachments responding to FDA Statistical RFI and submitted in 0005
12/29/2008	FDA	Acknowledgement	**FDA** letter accepting BLA application and identifying possible review issue regarding cardiovascular deaths and cardiovascular SAEs.
12/30/2008	FDA	Acknowledgement	FDA acknowledging receipt of the email 0005 submission and the electronic 0004 submission.
12/30/2008	SPI	Info Request/Clinical	**Submission 0005** - Response to 12/18/08 FDA Request for subgroup analyses by race for C0405 and C0406. submission provided Summary tables for C0405 and C0406 analyzing subjects by race, treatment regimens and the corresponding responses to the primary end
1/5/2009	FDA	PAI	Discussion regarding postponing PAI at BTG because of ongoing fight between Israel and Hamas; FDA stated that postponment will have no impact on ongoing BLA review, however, PAI is a requirement for BLA approval, and then the action date might be delayed
1/5/2009	FDA	Info Request/Clinical/Tox	FDA acknowledging receipt of Savient's response for info requested in FDA's 12/18/08 email re: the full PK/PD report for C0403 and also noting that FDA didn't think a formal submission was necessary - Clinical Pharmacology
1/6/2009	FDA	Info Request/CMC	FDA confirming it is okay to submit CMC changes as a single amendment as requested in Savient's 1/5/09 email.
1/7/2009	FDA	Info Request/CMC	FDA requesting contact information for Charles River Labs and Kendle and Savient's response on same date with this info.
1/16/2009	SPI	Amendment/CMC	**Submission 0006** - CMC update including analytical procedures because previous versions were submitted in original 0000 in error and providing new source documents for CMC sections 3.2.S.5, 3.2.P.3.3, 3.2.P. 3.4, 3.2.P.5.2, and 3.2. R.1.2
1/22/2009	FDA	Acknowledgement	FDA acknowledging that they received CMC Amendment 0006 and all files transmitted were ok.
1/22/2009	FDA	PAI	Contact Report to discuss January 289 - February 5, 2009 PAI at BTG under Israel's current situation., AAC Meeting scheduled for March and AAC agenda
1/23/2009	SPI	Info Request - Clinical	Email from M. Husain to Diana Walker providing explanation on various tables from ISS and ISE, Treatment Response by disease duration in study C0405/406 CSR Tables 10.11 and 10.12 and explanation of discrepancy in data in ISS and ISE. Provide a subgroup a
1/23/2009	SPI	REMS	Email from M. Husatin to Diana Walker providing outline of REMS tools to be submitted week of 2/2/09: HCP Intro Letter, HCGuide/Brochure,and Patient Guide
1/26/2009	FDA	Proprietary Name	FDA Letter, attached to email dated 1/27/09, accepting KRYSTEXXA
1/27/2009	SPI	REMS	Discussed submitting a revised REMS and Labeling to the BLA

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Date	From	Info Type	Description
1/27/2009	FDA	Proprietary Name	FDA Email from Diana Walker with FDA Acceptance Letter attached for our proposed propietary name, KRYSTEXXA
1/28/2009	SPI	Amendment/CMC	**Submission 0007** - Amendment to a Pending Application: CMC - based on agreement w/FDA at 11/21/06 Type B CMC mtg. to review Km and Kcat specs and additional stablity data prior to BLA approval, and at Pre BLA mtg. on 4/17/08, Div. also agreed Savient could
1/29/2009	SPI	Briefing Book	Discussed submitting reanalyzed data to the BLA and submitting a brief summary in the Briefing Book
1/29/2009	FDA	Amendment/CMC	FDA Email from Diana Walker acknowledging receipt of CMC Amendment 0007
1/29/2009	FDA	Info Request/Clinical	Email FDA Clinical Info Request ref ECGs and requesting that we send to FDA by Tuesday, 2/3/09.
1/29/2009	SPI	Info Request/CMC	Murad Husain will provide FDA with REMS Tools and revised labeling via e-mail by Friday, 1/30/09 followed by eCTD submission on Tuesday of following week
1/30/2009	SPI	Clinical/Labeling/BB	Submission of new PD analysis, CV adjudication and briefing book for AAC...Dr. Simon advised FDA of BLA oversight committee and discussed the organization of BLA and wanted to make more clear certain safety and efficacy information. Dr. Simon informed FDA
1/30/2009	SPI	Clinical/Labeling/BB	**VERSION 2:** Submission of new PD analysis, CV adjudication and briefing book for ACC...Dr. Simon advised FDA of BLA oversight committee and discussed the organization of BLA and wanted to make more clear certain safety and efficacy information. Dr. Simon i
2/1/2009	SPI	Briefing Book	Briefing Book dated February 1, 2009 for FDA AAC Meeting being held on March 5, 2009 at the Hilton in Silver Spring, MD. 35 CDs and 12 paper copies (hand delivered).
2/2/2009	SPI	Briefing Book	Receipt of SPI letter to Nicole Vesely with delivery of 12 paper copies of Briefing Book and 35 CD's with Briefing Book.
2/3/2009	FDA	Briefing Book	Email from Nicole Vesely suggesting 2 options for removing appendices from Briefing Book
2/4/2009	CRL	PAI	Letter from Charles River Labs to FDA confirming PAI for March 23 to 27, 2009
2/4/2009	SPI	Amendment/Clinical	**Submission 0008 –Response to FDA Requests for Information from January 23, 2009, Addendum to Risk Management Plan, Cardiac Adjudication and Revised Labeling** - request for an addendum to Risk Mgt. Plan and corresponding tools. Jan. 22, 2009 Tcon discussed
2/5/2009	SPI	Info Request/Clinical	TCON with FDA (Murad Hussain, SPI and Diana Walker, FDA) Purpose to discuss Revised REMS and Labeling.
2/6/2009	SPI	Amendment/Clinical	**Submission 0009** - Response to FDA Request for Information – Clinical- FDA 1/29/09 communications requesting we provide explanation how screening and Wk 25 ECGs were interpreted, requested a narrative explanation how categories were defined in Table A21
2/9/2009	FDA	PAI	Email from Oumou K. Barry, Associate Director, Field Investigations, FDA, informing us CRL confirmed 3/23/09 to 3/27/09 for inspection.
2/11/2009	FDA	120-Day Update	Email from FDA responding to request to delay 120-Day Safety Update by a week.
2/17/2009	FDA	Administrative	FDA Letter regarding extending PDUFA date to August 1, 2009
2/18/2009	FDA	Clinical	Email from FDA requesting submission of datasets and validation be submitted as a SAS transport file and received by FDA by Tuesday, 2/24/09
2/19/2009	FDA	Amendment/CMC	Email from FDA in response to Mfg qualification. FDA suggested we submit protocol to qualify alternative Mfg site for Pegloticase as a CMC Amendment to IND
2/24/2009	SPI	Info Request/CMC	Email from G. Savvas from CMC forwarding 3 attachments: Notification to CDER and OPD for Change of Sponsor Name and Importer for pegloticase DS (API).

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Date	From	Info Type	Description
2/25/2009	SPI	Administrative	Email from Mary Farbman regarding FDA Guide to International Inspection and travel
2/25/2009	FDA	Info Request/CMC	Email from Diana Walker, FDA, regarding upcoming comments from reviewers of CMC section of BLA
2/26/2009	FDA	Clinical	Email from Diana Walker agreeing to proposed timeline for Clinical (EKG and Cardiac Adjudication) submission on March 12, 2009
2/27/2009	SPI	Safety Update	**Submission 0010** - 120-day update to FDA in 0010
2/27/2009	SPI	Amendment/Clinical	**Submission 0011** - Response to Request for Information PK Data and datasets
2/27/2009	SPI	120-Day Update	**Submission 0012** - Error in Lifecycle Operator in 120-Day Safety Update
3/3/2009	SPI	Acknowledgement	Email from M. Husain confirming that Sequence 0012 is the correct 120-day safety update.
3/3/2009	FDA	PAI	FDA obtaining clearances for a June 3 - June 11 PAI at BTG. Will confirm at a later date
3/4/2009	FDA	PAI	Email from FDA thanking us for recommending the US Embassy Israeli Website for travel.
3/5/2009	FDA	Info Request/Clinical/Tox	BLA 125293 Nonclinical information request -- requesting amendment to Covance Report 7533-100 and final report regarding vacuoles
3/5/2009	FDA	Info Request/CMC	FDA requesting info regarding product quality and manufacturing Information Request - Microbiology CMC defiencies in BLA re: Fermentation steps, purification steps, PEGylation steps, formulation/filration...etc.
3/5/2009	FDA	Info Request/CMC	Email clarifying that info request in earlier 3/5/09 email should be submitted to Module 3.
3/10/2009	FDA	Acknowledgement	FDA Email stating that once 0013 is received she will forward to the Clinical Team
3/10/2009	SPI	Amendment/Clinical	Email to FDA with Cover Letter of 0013 regarding FDA questions on EKG - official submission sent on 3/10/09.
3/10/2009	SPI	Amendment/Clinical	**Submission 0013** - Response to Request for Information - Clinical CV Questions
3/13/2009	FDA	Info Request/CMC	Email from FDA requesting LOA from Sartorius DMF 5967, info and summary data for sterilization validation of 20L LDPE receiving bag, and info on integrity of bag's post-sterilization
3/17/2009	SPI	Info Request/CMC	Savient asking for clarification to Question 4b in Email dtd 3/5/09
3/18/2009	SPI	Info Request/Clin	Email stating 0014 cover letter and catheterization report is attached
3/18/2009	FDA	Info Request/CMC	FDA stating that Product Quality reviewer confirmed that Savient's response was sufficent in 3/17/09 email regarding question 4b re PEGylation steps.
3/18/2009	SPI	Info Request/CMC	Requesting FDA to grant a week delay in responding to 3/5/09 questions.
3/19/2009	FDA	Info Request/CMC	FDA confirming Savient can submit FDA info request - microbiology on April 3. Also FDA requested clarification on PI, Savient changed section 17.3 to Medication Guide...ok w/FDA but wanted to clarify our intent.
3/19/2009	SPI	Amendment/Clinical	**Submission 0014** - Response to RFI - Clinical
3/20/2009	SPI	Info Request/CMC	Responding to 3/19/09 email thanking for extension for CMC Amendment filing and Savient response re error in PI.
3/20/2009	FDA	Info Request/CMC	FDA responding to 3/20/09 email reference CMC comments from reviewers and PI error. Ms. Walker going to talk with Dr. Siegel and suggesting we wait and make corrections/rev. during labeling discussions to cut down on number of submisisons and confusion.
3/23/2009	SPI	Info Request/CMC	Savient requesting names of primary microbiology reviewer and supervisory reviewers for BLA.
3/24/2009	FDA	Info Request/CMC	FDA responding that if Savient needs to communicate with reviewers, to let Ms. Walker know and she will arrange a TCON.

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3/25/2009	SPI	Info Request/CMC	Savient responding to Division recommendations to add 0.2 um filters and requesting a brief Tcon with Review Microbiogist and CMC reviewers.
3/27/2009	FDA	Info Request/CMC	FDA responding to 3/24/09 email and responding to the 2 questions in that email (0.2up filtration, and commercialization of six lots...)
3/30/2009	SPI	PAI	Savient sent updated BTG Mfg. schedule for PAI in June.
3/31/2009	FDA	PAI	FDA confirmed receipt of updated Mfg schedule, stated no further requests and send schedule as amendment to BLA.
4/3/2009	SPI	Administrative	Email from Mary Farbman requesting Savient to make hotel reservations for PAI at BTG...M. Husain responding on same date confirming that Savient will be happy to do so.
4/3/2009	SPI	Amendment/CMC	Email to FDA confirming Savient will arrange hotel reservations and ground transportation.
4/3/2009	SPI	PAI	Email to FDA forwarding copy of Sequence 0016 cover letter which provides the Mfg. schedule for upcoming PAI in June 2009. See Sequence 0016 for cover letter attached to email.
4/3/2009	SPI	Amendment/CMC	**Sequence 0015** - Response to FDA Request for Information-CMC/Microbiology
4/3/2009	SPI	Amendment/CMC	**Sequence 0016** - Manufacturing Schedule for Pegloticase Drug Substance for Pre-Approval Inspection (2009) at BTG
4/6/2009	FDA	Acknowledgement	FDA acknowledging receipt of Sequence 0015 and 0016 and that they were forwarded to the appropriate review team members.
4/8/2009	SPI	Amendment/Clinical	**Sequence 0017** - Submitted to FDA Audited final immunohistochemistry report - PAI Study No. IM1678 as an amendment to Covance 7533-100 and a Summary Report prepared by Hugh Black
4/17/2009	FDA	Info Request/CMC	Product Quality & Mfg Info Request - Microbiology CMC deficiences - Drug Product: Issue 1. confirm psi pressure inside vessel (PPD); Issues 2-3 provide summary data: for validtion info on more challenging microbial ingress study re media fill run #8171, t
4/17/2009	SPI	PAI	Savient sending to FDA reassessed mfg schedule for June PAI.
4/17/2009	FDA	PAI	Savient sending to FDA reassessed mfg schedule for June PAI.
4/20/2009	SPI	Administrative	Email from M. Husain to P. Hamelin regarding conversation with FDA, Diana Walker, regarding upcoming submissions and her response (mfg. schedule, REMS. EKGs) .
4/20/2009	SPI	Administrative	M. Husain informing FDA re: upcoming submissions (mfg schedule, report on EKGs, revised REMS, and request for TCON re BB and presentation at AAC.
4/21/2009	SPI	Administrative	Email to FDA forwarding copy of Sequence 0020 cover letter. (See Sequence 0020)
4/21/2009	SPI	Amendment/CMC	**Sequence 0018** - Revised mfg. schedule for June BTG PAI
4/21/2009	SPI	Amendment/Clinical	**Sequence 0019** - Per 3/10/09 communication responding to Agency request to review abnormal exit EKG...submitting QT study from independent cardiologist of all EKGs for C0405 & C0406.
4/22/2009	SPI	Administrative	**Sequence 0020** - Points for Discussion prior to the AAC Mtg.: focus of communication is the disseminationof key elements of AAC BB and AAC presentation. Submission included questions to help in preparation for upcoming TCON.
4/27/2009	FDA	Administrative	FDA confirming TCON for 4/29/09 at 1 pm (EST).
4/28/2009	SPI	Info Request/CMC	Sending an advance copy of Sequence 21 letter requesting TCON to discuss KM/kcat assay.
4/28/2009	SPI	ACC	Savient sending revised list of consultants attending AAC mtg.
4/29/2009	FDA	ACC	FDA initiated: FDA's response to Savient questions submitted on 4/21/09 about the briefing book and upcoming AAC meeting.
4/29/2009	FDA	Acknowledgement	FDA acknowledging receipt of 4/28/09 email and stating they will forward Sequence 21 letter to CMC team re TCON.
4/29/2009	SPI	Amendment/CMC	**Sequence 0021**- Request for CMC Teleconference w/FDA CMC review team to discuss the KM/kcat assay...

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5/5/2009	FDA	Administrative	Email from FDA responding to 0021 request for TCON...CMC reviewers do not feel it is neessary at this time. See 4/28/09 email to FDA sending copy of Sequence 0021.
5/5/2009	SPI	Info Request/CMC	FDA requested location of info in BLA in 5/5/09 email and Murad responded with location on same date...see email chain.
5/6/2009	FDA	ACC	Email from FDA reminding Savient that AAC background package due to FDA on 5/14/09 and Savient's acknowledging receipt of response and othe emails re AAC meeting.
5/6/2009	FDA	ACC	Email from N. Vesley w/attached list of Savient consultants attending AAC in June.
5/7/2009	FDA	ACC	FDA (N. Vesely) responding to M. Husain 5/6/09 email asking when FR announcement will be published and noting it will officially publish 5/8/09...also providing mtg room set up, materials needed and FDA requesting names and affiliations of speakers by Jun
5/7/2009	FDA	ACC	Email from FDA informing Savient that they don't provide INR with background package for AAC meeting and informing Savient that Dr. D. Bruce Burlington will be the IR at meeting.
5/8/2009	SPI	Info Request/CMC	Savient asking FDA for clarification of Question #2 in 4/17/00 email regarding CMC info requestt
5/11/2009	SPI	Info Request/CMC	Savient asking again if CMC reviewer could provide clarification to Q2 in 4/17/09 FDA email info req.
5/12/2009	SPI	Info Request/CMC	**Sequence 0022** - Response to FDA Request for Information CMC/Microbiology.
5/14/2009	SPI	Briefing Book	Briefing Document for Arthritis Advisory Committee Meeting, June 16, 2009
5/18/2009	FDA	Info Request/CMC	FDA CMC responding to Savient request for clarification re Q2 in 5/8/09 email.
5/18/2009	FDA	Info Request/CMC	Chain of emails 5/18/09 through 4/17/09 (G. Zhu) with FDA subject: "Refusal of Admission" on Entry #231-96095445"...FDA informing Savient Compliance officer contacted and it is still under review.
5/19/2009	FDA	PAI	FDA Letter emailed with EIR for East Brunswick NJ covering conduct of clinical study C0405 and C0406
5/28/2009	FDA	Info Request/CMC	Email from FDA re Chemistry/Product information request and requesting info by no later than June 11, 2009.
5/29/2009	SPI	Info Request/CMC	Email responding to FDA's 5-28-09 Chemistry Info Request email and seeking clarification of the FDA's request.
5/29/2009	SPI	PAI	Email from Savient responding to FDA's 5/27/09 email regarding travel info and logistics for upcoming PAI BTG inspection first week of June 2009. (See chain of emails)
6/1/2009	FDA	Info Request/CMC	Email from FDA responding to Savient 5/28/09 chemistry clarification.
6/3/2009	FDA	Info Request/CMC	Email from FDA requesting Microbiology CMC deficiencies for Savient BLA, STN 125293/0: Drug Product to be submitted to the FDA no later than Wednesday, June 17, 2009
6/4/2009	SPI	Briefing Book	Letter to FDA w/attachments - Errata to FDA Briefing Book and Errata to Savient briefing book for Arthritis Advisory Committee meeting scheduled for June 16, 2009.
6/11/2009	SPI	Info Request/CMC	Email to D. Walker at email attaching the cover letter for Sequence 0023 and informing the FDA it will be formally submitted today by the gateway.
6/11/2009	FDA	Info Request/CMC	FDA email acknowledging timely submission to their June 1, 2009 Chemistry clarification request responses.
6/11/2009	SPI	Amendment/CMC	**Sequence 0023** - Reponse to FDA request for information- CMC reference the FDA's May 28, 2009 Email requesting clarification of information provided in BLA and subsequent amendments.
6/12/2009	FDA	General Correspondence	Email from FDA regarding FDA presentation slides before teleconference

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6/15/2009	FDA	General Correspondence	Email from FDA confirming they will correct BLA # error and re-post correct # on website. FDA responding to Savient's June 14, 2009 email informing them of error which is part of this email chain.
6/15/2009	FDA	Briefing Book	Email from FDA with Addendum to their briefing package
6/17/2009	SPI	Info Request/CMC	Email to FDA responding to June 3, 2009 email requesting Microbiology Information Request. This email responds to FDA comments 1, 3, 4, 5, and 6 in the June 3, 2009 email. Response to comment #2 will be submitted with formal amendment.
6/17/2009	SPI	PAI	Email to FDA confirming FDA's requested items, sending list of items discussed and Savient requesting FDA's confirmation that the proposals to fulfill these requested items are accurate and acceptable.
6/18/2009	FDA	PAI	Email from FDA, Diana Walker, confirming she has forwarded our email dated 6/17/09 "Requested Items form Dr. Farbman" to Dr. Farbman. Dr. Farbman will contact us with her comments to our responses.
6/18/2009	FDA	PAI	Email from FDA Diana Walker, items 1 through 8 being reviewed, Dr. Farbman confirmed that items 9, 10, and 11 are required and request we submit them by email followed by official submission.
6/18/2009	SPI	Info Request/CMC	Email with response to Microbiology Request sent in Sequence 0024
6/18/2009	SPI	Info Request/CMC	Email attaching Items 9, 10, and 11 requested by M. Farbman of FDA.
6/18/2009	SPI	Amendment/CMC	**Sequence 0024** - Response to FDA Request for Information - CMC (see June 3, 2009 email from D. Walker at FDA requesting clarifications of microbiological info provided in BLA)
6/19/2009	SPI	Info Request/Clinical	Email to FDA ref June 17 2009 Immunology Information request...formal submission Sequence # 0025 will be submitted on June 22, 2009 (this file includes attachment)
6/22/2009	SPI	Amendment/Clinical	**Sequence 0025** - Amendment - Clinical in response to June 17, 2009 FDA request. Savient provided Interim Progress Report of Anti-uricase Antibody Assays in Two Phase 3 Clinical Studies (C0405 & C0406).
6/23/2009	FDA	Info Request/CMC	Email from FDA confirming when to submit specific documents described in Sequence 0024 in table on Page 6.
6/23/2009	SPI	Amendment/CMC	**Sequence 0026** - Response to FDA Request for Information - CMC - Responding to FDA June 18 and 19, 2009 emails. Submitting list of submission timelines and documents requested by Dr. M. Farbman from FDA at PAI during BTG in June 2009.
6/24/2009	FDA	Info Request/CMC	TCON initiated by FDA: Purpose: Peglylation Process difference between Phase 3 Clinical and Comercial Batches - ref FDA's email dtd. June 19, 2009.
6/25/2009	FDA	General Correspondence	Email chain on 6/25/09 regarding FDA having problems with ESG receiving submissions. This chain of emails is regarding Sequence 0027. Diana Walker informing M. Husain that she was notified the FDA had received sequence 0027 at 2:43 pm on 6/25/09.
6/25/2009	SPI	Amendment/CMC	**Sequence 0027** - Responding to FDA June 23, 2009 email requesting submission of remaining four documents under items 1, 2, 3, and 5 previously tabulated in Sequence 0024. See Sequence 0026, 0024 and 0015 for all documents requested by FDA. Document associ
6/26/2009	FDA	Info Request/CMC	CMC Information request - Reference batch 568200310...reviewers requesting Savient to address comparability issues between products...
6/26/2009	SPI	Amendment/Clinical	**Sequence 0028** - Response to FDA Request for Information - Clinical - ref stopping rule..
6/29/2009	FDA	Info Request/CMC	Email from FDA ref Savient request for TCON to discuss FDA 6/26/09 email regarding CMC issues.
6/30/2009	FDA	Info Request/CMC	Email from FDA Microbiology Information Request...requesting deficiencies to be addressed with an amendment to the BLA
7/1/2009	FDA	Info Request/Post Marketing	FDA Request for Information/potential PMR proposals

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Date	From	Info Type	Description
7/1/2009	FDA	Labeling	Email from FDA regarding draft label.
7/7/2009	SPI	Info Request/Post Marketing	Email requesting clarity regarding July 1, 2009 email regarding post-marketing proposals.
7/8/2009	FDA	Info Request/Post Marketing	Email from FDA responding to 7/7/09 Savient email asking for clarity regarding PMR proposals...Dr. Siegel responded to questions 1 and 4 and Dr. Mellon will discuss # 2 during TCON.
7/8/2009	SPI	Amendment/CMC	**Sequence 0029** Response to FDA Request for Information - CMC and Stability Update - commitment made to Agency at Type B CMC Mtg on 11/21/2006, submitting real time stability data for the drug product for up to 24 mons...
7/9/2009	FDA	Info Request/CMC	Email from FDA requesting timeline for Savient's response to the agency's June 30, 2009 microbiology information request. This is a chain of emails dtd 7/9/09 responding to that request and why the delay and informing FDA that Savient will respond on 7/1
7/10/2009	FDA	Info Request/Post Marketing	FDA initiated: Post-marketing required (PMR): Toxicology Study
7/10/2009	SPI	Labeling	Email to FDA forwarding Clean copy of draft labeling per July 1, 2009 FDA request and forwarding draft PI Labeling per July 1, 2009 FDA request. (See July 1, 2009 email from FDA)
7/10/2009	SPI	Info Request/CMC	Email to FDA in response to FDA's June 26, 2009 request for CMC information...also included dial in numbers for July 13, 2009 TCON with FDA.
7/10/2009	SPI	Amendment/CMC	Email from Savient forwarding a copy of Sequence 0030 coverletter.
7/10/2009	SPI	Amendment/CMC	**Sequence 0030** - Response to FDA Request for Microbiology Information...responding to June 30, 2009 email from FDA requesting additional microbiological in-process controls in the drug substance mfg. process.
7/13/2009	SPI	Info Request/Post Marketing	Email responding to FDA July 1, 2009 email request for information/potential PMR Proposals - two requests for post-marketing proposals from the Division, Clinical and Non-Clinical. (Email chain includes July 1, 2009 email from FDA)
7/15/2009	FDA	General Correspondence	Email from FDA responding to 7/15/09 email from M. Husain requesting status of CMC info req, labeling group, and PI. FDA provided an update regarding these issues. (See July 15. 2009 email chain with FDA)
7/15/2009	FDA	General Correspondence	Email chain between FDA and Savient regarding status of items...FDA indicating that the CMC info requests submitted by email may not need to be submitted as formal amendments to BLA. Responding to M. Husain's inquiry of July 15, 2009...(See email chain)
7/15/2009	FDA	General Correspondence	Email from FDA...CMC/Product requested that we submit CMC responses as amendment for the record. (See Sequence 0031)
7/17/2009	SPI	Amendment/CMC	Email to FDA forwarding formal Sequence 0031 Amendment cover letter to FDA as requested in the July 15, 2009 email.
7/17/2009	SPI	Amendment/CMC/ Clinical	**Sequence 0031-** Response to FDA Request for CMC Information: Responding to June 26, 2009 email from FDA requesting Savient to address 4 CMC Comments regarding batches of KRYSTEXXA.
7/27/2009	FDA	General Correspondence	Responding to telephone message regarding status of several items, including Action letter.
7/29/2009	FDA	Acknowledgement	FDA initiated: Heads-up for PDUFA action.
7/31/2009	FDA	General Correspondence	Email from FDA Forwarding Action letter for BLA 125293. Original ltr sent via US mail.
7/31/2009	FDA	General Correspondence	FDA's Complete Response Letter regarding approval of Krystexxa.
8/6/2009	FDA	General Correspondence	Email from FDA clarifying what we need to include in our meeting request.

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8/6/2009	FDA	General Correspondence	FDA respond acknowledging 8/6/0-9 email from Savient forwarding copy of our Type A Meeting Request letter...official submission will follow.
8/6/2009	SPI	General Correspondence	Savient responding to 8/6/09 FDA email tentatively scheduling 9/14/09 Type A Meeting Requst.
8/6/2009	SPI	Administrative	**Sequence 0032** Request for a Type A Meeting- requesting meeting to address issues in CRL
8/7/2009	SPI	General Correspondence	Savient confirming that they prefer September 14 for Type A meeting
8/10/2009	FDA	Efficacy Supplement	FDA inquiring if we are submitting mtg request week of 8/10/09
8/10/2009	SPI	General Correspondence	Savient informing FDA official meeting request sent by ESG
8/10/2009	FDA	General Correspondence	FDA acknowledging receipt of mtg request through Gateway
8/10/2009	FDA	General Correspondence	Letter from FDA granting Type A Meeting, scheduled for 9/14/09
8/11/2009	FDA	General Correspondence	FDA email frowarding copy of Meeting Granted letter dtd. August 10, 2009...original will be received by mail. (See 8/10/09 entry below)
8/24/2009	FDA	Info Request/CMC	Email from FDA: TCON 8-27 discussin topics: OLE lots, reference the 12 lots of drug substance with high levels of bioburden, and requesting we describe intentions Ph 3 mfg process or conduct bridging studies linking the Ph 3 materials, etc.
8/25/2009	SPI	General Correspondence	**Sequence 0033** Type A Meeting: September 14, 2009 Briefing Document - outlining specific objectives and outcomes for discussion at 9/14/09 mtg. and includes the hard copies and CDs of the briefing materials for meeting.
8/26/2009	SPI	Info Request/CMC	Email to FDA responding to their 8/24/09 email regarding 8/27/09 TCON Disc. Topics and responding to requests regarding Drug Product Lots, BLA resubmission plans , dial in #'s for TCON and who from Savient will participate in TCON on 8/27/09.
8/27/2009	FDA	Info Request/CMC	FDA initiated: Restriction on Manufactured DP Batches
8/27/2009	FDA	Info Request/CMC	Email from FDA after 8/27/09 TCON requesting Savient to state verbal commitment to destroy/discard any batches/lots of drug that havehigh bioburen levels and to submit as an amendment to BLA.
9/2/2009	SPI	Info Request/CMC	Email to FDA provide clarity and relevant information regarding the FDA's request in e-mail dated 27 August 2009 for Savient to destroy certain pegloticase Drug Product batches (12 batches of Process B Drug Substance)...etc.
9/11/2009	FDA	Administrative	Email from FDA forwarding official ltr attaching division's responses to Savient's questions from meeting package for 9/14/09 Typa A Meeting.
9/11/2009	SPI	Administrative	Email to FDA thanking for responses to sponsor's questions for type A meeting on 9/14/09 and confirming that sponsor does not want to change anything regarding that mtg.
9/11/2009	FDA	Administrative	Email from FDA reference Mass Spectra...attaching Appendix I Mass Spectra...FDA acknowleding we submitted this information on July 10, 2009 according to their info request dtd June 26, 2009.
9/11/2009	FDA	Administrative	FDA letter with Division's responses to Savient's questions from meeting package for 9/14/09 Type A Meeting.
9/13/2009	SPI	Administrative	Attaching word copy of list of topices that sponsor would like to review at 9/14/09 Type A Meeting. (Attachment included with link)
9/18/2009	FDA	Administrative	Email from FDA: Advice on REMS Submission 18Sep09 - comments for Sponsor from office of Surveillance & Epidemiology, DRISK, ref REMS proposal in Savient's briefing package provided for 9/14/09 Type A Mtg. Comments were in ref to REMS Goals, Medication Gu
9/22/2009	SPI	Administrative	**Sequence 0034** Type A Meeting Minutes with Sponsor's comments

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9/25/2009	SPI	Amendment/CMC	**Sequence 0035** Disposition of Drug Product Batches - sponsor committing to destroying batches with high bioburden and summarizing what it will do with the remaining in quarantine at Enzon or Fisher Clinical Svcs.
10/6/2009	FDA	Administrative	FDA sending official copy of September 14, 2009 Type A Mtg. minutes.
11/18/2009	SPI	General Correspondence	Email sending copy of Sequence 0036 regarding Type A Meeting Minutes: Proposal for Revision.
11/18/2009	SPI	General Correspondence	**Sequence 0036 Type "A" Meeting Minutes: Proposal for Revision:** Requesting a modification of minutes from 9/14/09 meeting minutes.
12/14/2009	FDA	General Correspondence	FDA reviewers' agreed to Savient's Meeting Minutes revisions for Type A Meeting. Formal letter will be issued in Jan 2010.
1/11/2010	FDA	General Correspondence	Email from FDA forwarding letter regarding their response to Sequence 0036 Type A Meeting Minutes: Proposal for Revision.
1/11/2010	FDA	General Correspondence	Letter from FDA regarding request for modification of minutes for 9/14/09 meeting, and agree to the proposed mofication of minutes in Question 2c of those minutes...
2/5/2010	FDA	General Correspondence	Email from FDA confirming formatting of revisions for resubmission.
3/9/2010	SPI	General Correspondence	TCON to inform FDA about BLA resubmission Week of March 15, delay of pegloticase IND AR. During TCON FDA informed Svt of FDA restructure.
3/11/2010	FDA	Administrative	Intro to new project manager at FDA, Badrul Chowdhury
3/12/2010	FDA	Administrative	FDA confiming name and address of new Director, Badrul Chowdhury.
3/15/2010	SPI	General Correspondence	Email to FDA informing we sent Seq. 0037 BLA resubmission through FDA Gateway through eCTD vendor ISI.
3/15/2010	SPI	Info Request/Clinical/CMC	**Sequence 0037 Response to the July 31, 2009 Complete Response Letter** - provide additional CMC info and a Safety Update, including Labeling, REMS, and Medication Guide according to mutual agreements reached at Type A mtg between FDA and SPI in Sept 2009.
3/17/2010	FDA	Acknowledgement	FDA confirming receipt of Sequence 0037 BLA resubmission
3/29/2010	FDA	Acknowledgement	FDA emailing a copy of "Acknowledge Complete Response" letter indicating they received and accepted BLA resubmission and consider this a complete, class 2 response to the FDA action letter...and that 9/14/10 is the user fee goal date.
3/29/2010	FDA	Acknowledgement	FDA "Acknowledge Complete Response" letter indicating acceptance and designating the BLA resubmission as a Class 2 review with PDFA date of 9/14/10.
4/12/2010	SPI	Administrative	Email contact report from S Hamburger regarding voicemail request from FDA T. Phlhaus asking for the name of the Head of the Eurosequence facility.
4/14/2010	SPI	Administrative	Email contact report from S. Hamburger informing staff that he provided T. Pohlhuas of FDA with the Henk J. Bak, PhD, contact information.
4/15/2010	FDA	General Correspondence	Email from FDA reference Savient's request to clarify 2 questions related to the April 14, 2010 request from FDA when preparing the reply (see Submission, Sequence 0038) (Email chain beginning 4/7 and ending with 4/15/10 emails regarding IR 1 & 2)
4/23/2010	SPI	General Correspondence	**Sequence 0038 General Correspondence: Response to Apr 14, 2010 E-Mail Requests** to provide a brief summary to each issue identified in CRL and provide changes made to the CMC portion that were not part of the response to CRL.
5/21/2010	SPI	General Correspondence	Email forwarding S. Hamburger's email to FDA with letter from BTG dtd. 5/20/10 letter informing FDA corrective actions for the observations in Form FDA 483 from PAI June 2009 have been completed except for ongoing studies.

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5/25/2010	SPI	General Correspondence	Email from S. Hamburger forwared by M. Husain to FDA R. Sista, to provide clarification of CMC items tofacilitate the FDA review of KRYSTEXXA.
5/25/2010	FDA	Info Request/CMC	Email from FDA: BLA 123293-Peglotiase IR-3 - Requesting CMC microbiology information by noon of June 1, 2010.
6/1/2010	FDA	General Correspondence	FDA responding to 5-25-10 email requesting clarification regarding 3 Month CMC update and other issues with CMC
6/1/2010	SPI	General Correspondence	**Sequence 0039: General Correspondence: Response to May 25, 2010 E-Mail Requests** regarding validation of equipment
6/4/2010	FDA	Info Request/CMC	Information Request 3 - FDA requesting by COB 6/25/10 a study of the PennTech vial washer be done to provide uantitative data demosnstrating rmeovel of spiked sodium chloride on KRYSTEXXA vials from 3 wash cycles.
6/7/2010	SPI	General Correspondence	**Sequence 0040 General Correspondence: CMC Update** amendment replacing Regional Information Section CTD 3-2-R -updating Table 3 of leaf because BTG updated manufacturing SOPs and in Sequence 0037, Table 3 Savient inadvertently did not include a few SOP r
6/16/2010	SPI	General Correspondence	**Sequence 0041 General Correspondence: Response to FDA Request on Vial Washer** - responding to Division's June 4, 2010 email request regarding PennTech vial washer at Sigma-Tau PharmaSource...
7/1/2010	SPI	General Correspondence	Subject: KRYSTREXXA BLA review cycle questions...asking for TCON to confirm the new divisions timeline regarding our responses to the FDA's information requests.
7/2/2010	SPI	General Correspondence	**Sequence 0042 General Correspondence: Response to FDA Request on Vial Washer** - Questions to FDA regarding SigmaTau PharmaSource's to provide report with info regarding sodium chloride; requesting agreement to submit report in ealry August 2010 regarding
7/12/2010	SPI	General Correspondence	Pegloticase: Specific Activity, KM and kcat by Product Accumulation and KM and kcat by Substrate Depletion assays (Acceptance criteria) - Information
7/13/2010	SPI	Administrative	Email from S. Hamburger to P. Hamelin, M. Husain, P. Yachmetz, P. Clarke regarding phone mail message to FDA, Dr. Sista asking for feedback to Savient's Jul 1, 2010 email request related to the status of the review from all disciplines and regarding email
7/13/2010	FDA	General Correspondence	Edmail responding to July 1, 2010 email from S. Hamburger regarding KRYSTEXXA BLA review cycle questions.
7/20/2010	SPI	General Correspondence	Email to R. Sista at FDA regarding Savient's Key questions for BLA review, e.g., PAI of BTG facility scheduling, 483 for Eurosequencing and other CMC questions.
7/21/2010	SPI	Administrative	Email to P. Hamelin, P. Yachmetz, P. Clarke regarding voicemail message to Dr. Sista at FDA: Phone call notes to Dr. Ramani Sista (FDA): 21 July 2010 Regarding 20 July 2010 email questions.
7/27/2010	SPI	Administrative	Email to FDA regarding phone message made by S. Hamburger to Dr. Sista of FDA informing her that the Updated Stability Data would be submitted on Wednesday, July 28, 1010.
7/28/2010	SPI	General Correspondence	**Sequence 0043 General Correspondence: Updated Stability Data** (3- 6 months stability updated data)
7/29/2010	SPI	Administrative	**FDA Contact: July 29, 2010** - To P. Hamelin, P. Clarke, P. Yachmetz, M. Husain - S. Hamburger called FDA and left vm and at 1:45 PM FDA/Dr. Sista returned call. She inquired if we had started the 18-month dog study and was informed Savient had not although
7/30/2010	FDA	General Correspondence	**FDA Email** responding the Key Questions from Savient Regarding KRYSTEXXA (pegoloticase) BLA review...FDA responses follow al ter each questions in Savient's 7/20/10 email
7/30/2010	SPI	General Correspondence	**Savient email** acknowledging receipt of the 7/30/10 email from FDA regardidng key questions.
7/30/2010	FDA	General Correspondence	**FDA email** responding to Q7 as promised in earlier 7/30/email from Dr. Sista, FDA (Key Questions from Savient to FDA)

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8/4/2010	SPI	General Correspondence	**Sequence 0044: General correspondence: Response to FDA Request for Additional Data for PennTech Vial Washer** submitted final reports for the PennTech Vial Washser fro SigmaTau Pharmaceuticals.
8/4/2010	SPI	Administrative	S. Hamburger to P. Hamelin, P Yachmetz, M Husain, and P Clarke....called FDA and left VM regarding Sequence 0044 was sent on this date and which FDA requested be submitted by 8/6/10 and to inform h=them regarding the status of the assay from Eurosequence
8/13/2010	SPI	Administrative	**Phone Contact: August 13, 2010 10 am.**: S.Hamburer left vm with Dr. Sista requesting time to discuss logistics regarding the next 30 days before the 9/14/10 PDUFA date.
8/18/2010	SPI	Administrative	**Email** from QA at Savient regarding FDA inspection at Core Labs...confirming inspection finished and no 483's received.
8/30/2010	FDA	General Correspondence	FDA DMEPA completed their review of cart and container lables and PI and identified deficiencies... see Sequence 0047 for response.
9/2/2010	SPI	General Correspondence	**Sequence 0045 - GENERAL CORRESPONDENCE: Withdrawal of Qualification Protocols for Pegloticase and Uricase Reference Standard** (PRT-QA-074, BLA Section 3.2.s.5 and PRT-QA-075, BLA Section 3.2.s.5)
9/2/2010	SPI	General Correspondence	**Sequence 0046 - GENERAL CORRESPONDENCE: Letter of Intent to Perform CMC Post Marketing Commitments and Phamracology/Toxicology Post Marketing Requirements**
9/3/2010	SPI	General Correspondence	Sequence 0047- GENERAL CORRESPONDENCE: Response to Discipline Rview: Carton Lables (outer and Inner), Peel-off Label and Container Label
9/8/2010	SPI	General Correspondence	**Sequence 0048 - General Correspondence: Updated Letter of Intent to Perform CMC Post Marketing Commitments and Pharmacology/Toxicology Post Marketing Requirements** (See Sequence 0046 too)
9/8/2010	SPI	General Correspondence	**Sequence 0049 - General Correspondence: Letter of Intent to Perform Clinical Post Marketing Requirements**
9/10/2010	SPI	General Correspondence	**Sequence 0050 - General Correspondence:Final Draft KRYSTEXXA Carton labels (outer and inner), Peel-off Label and Container Label; Final Draft KRYSTEXXA Medication**
9/14/2010	SPI	General Correspondence	**Sequence 0051 - General Correspondence: Final KRYSTEXXA Full Prescribing Information**
9/14/2010	SPI	General Correspondence	**Sequence 0052 - General Correspondence: Letter of Intent for CMC, Clinical and Non-clinical Pharmacology/Toxicology Post Marketing Requirements/Commitments**
9/14/2010	SPI	General Correspondence	**Sequence 0053 - General Correspondence: Final REMS and Attachments AND REMS Supporting Document**
9/14/2010	FDA	General Correspondence	**BLA Approval**

TO THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re United States Patent No. 6,783,965
Granted: August 31, 2004

Patentees: Merry R. Sherman, Mark G. P. Saifer, L. David Williams, Michael S. Hershfield, Susan J. Kelly

Assignees: Mountain View Pharmaceuticals, Inc.
Duke University

For: Aggregate-free urate oxidase for preparation of non-immunogenic polymer conjugates

Commissioner for Patents
U.S. Patent and Trademark Office
Mail Stop Patent Ext.
Randolph Building
401 Dulany Street
Alexandria, VA 22314

APPLICATION FOR EXTENSION OF PATENT TERM
PURSUANT TO 35 U.S.C. § 156

Sir:

Pursuant to Section 201(a) of the Drug Price Competition and Patent Term Restoration Act of 1984, 35 U.S.C. § 156(a), Mountain View Pharmaceuticals, Inc. and Duke University (collectively, "Applicants") hereby request an extension of the patent term of United States Patent No. 6,783,965 ("the '965 Patent").

Applicants represent that they are the record owners of the entire interest in the '965 Patent, by virtue of assignments from the inventors thereof recorded in the United States Patent and Trademark Office (Reel/Frames: 10836/0572-0574 and 17663/0313-0315) with respect to the patent application leading thereto as documented in **Exhibit 1** hereto.

Inquiries and correspondence relating to this application are to be directed as set forth in section (15) below.

The holder of marketing approval for KRYSTEXXA™ (pegloticase), the Approved Product that is relevant to this application, is Savient Pharmaceuticals, Inc. of East Brunswick, New Jersey, the exclusive licensee of the '965 Patent. Applicants are authorized to rely upon the activities of Savient Pharmaceuticals, Inc. before the U.S. Food and Drug Administration ("FDA") for this application for extension of patent term of the '965 Patent as documented in **Exhibit 2** hereto.

The following information is submitted in accordance with 35 U.S.C. § 156(d) and 37 C.F.R. § 1.710 et seq., and for the convenience of the United States Patent and Trademark Office, the information in this application is presented in the order and format as set forth in 37 C.F.R. § 1.740(a):

(1) **A complete identification of the approved product as by appropriate chemical and generic name, physical structure or characteristics;**

The Approved Product, KRYSTEXXA™ (pegloticase), is a PEGylated uric acid specific enzyme for administration by intravenous infusion for the treatment of chronic gout in adult patients refractory to conventional therapy. Gout refractory to conventional therapy occurs in patients who have failed to normalize serum uric acid and whose signs and symptoms are inadequately controlled with xanthine oxidase inhibitors at the maximum medically appropriate dose or for whom these drugs are contraindicated.

The chemical names of KRYSTEXXA include: Oxidase, urate (synthetic *Sus scrofa* variant pigKS-ΔN subunit), homotetramer, amide with α-carboxy-ω-methoxypoly(oxy-1,2-ethanediyl); and des-(1-6)-[7-threonine,46-threonine,291-lysine,301-serine]uricase (EC 1.7.3.3, urate oxidase) *Sus scrofa* (pig) tetramer, non acetylated, carbamates with α-carboxy-ω-methoxypoly(oxyethylene). The peptide monomer sequence of KRYSTEXXA is:

```
TYKKNDEVEFVRTGYGKDMIKVLHIQRDGKYHSIKEVATTVQLTLSSKKD     50

YLHGDNSDVIPTDTIKNTVNVLAKFKGIKSIETFAVTICEHFLSSFKHVI     100

RAQVYVEEVPWKRFEKNGVKHVHAFIYTPTGTHFCEVEQIRNGPPVIHSG     150

IKDLKVLKTTQSGFEGFIKDQFTTLPEVKDRCFATQVYCKWRYHQGRDVD     200

FEATWDTVRSIVLQKFAGPYDKGEYSPSVQKTLYDIQVLTLGQVPEIEDM     250

EISLPNIHYLNIDMSKMGLINKEEVLLPLDNPYGKITGTVKRKLSSRL      300
```

Approximately 10 out of the 30 lysine residues of the peptide monomer are PEGylated.

See Approved Label attached as **Exhibit 3** with regard to the statements in this Section (1).

(2) A complete identification of the Federal statute including the applicable provision of law under which the regulatory review occurred;

The Approved Product is a drug product and the submission was approved under Section 351 of the United States Public Health Service Act (42 U.S.C. § 262).

(3) An identification of the date on which the product received permission for commercial marketing or use under the provision of law under which the applicable regulatory review period occurred;

The Approved Product KRYSTEXXA™ received permission for commercial marketing or use under Section 351 of the Public Health Service Act (42 U.S.C. § 262) upon approval of Biologics License Application ("BLA"), STN: BLA 125293, on September 14, 2010.

A copy of the FDA approval letter is attached as **Exhibit 4**.

(4) In the case of a drug product, an identification of each active ingredient in the product and as to each active ingredient, a statement that it has not been previously approved for commercial marketing or use under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act, or a statement of when the active ingredient was approved for commercial marketing or use (either alone or in combination with other active ingredients), the use for which it was approved, and the provision of law under which it was approved.

As active ingredient, a single dose of the Approved Product KRYSTEXXA™ contains a clear, colorless, sterile 8 mg/mL solution of pegloticase in a 2 mL single-use vial, expressed as amounts of uricase protein.

Neither the Approved Product KRYSTEXXA™ nor the active ingredient pegloticase has been previously approved for commercial marketing or use under the Food, Drug, and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act.

(5) A statement that the application is being submitted within the sixty day period permitted for submission pursuant to §1.720(f) and an identification of the date of the last day on which the application could be submitted;

KRYSTEXXA™ was approved on September 14, 2010, and the last day within the sixty day period permitted for submission of an application for patent term extension is November 12, 2010, which is subsequent to the date on which this application has been submitted.

(6) A complete identification of the patent for which an extension is being sought by the name of the inventor, the patent number, the date of issue, and the date of expiration;

Name of the inventors:	Merry R. Sherman, Mark G. P. Saifer, L. David Williams, Michael S. Hershfield, Susan J. Kelly
Patent number:	6,783,965
Date of issue:	August 31, 2004
Date of expiration:	August 6, 2019

(7) A copy of the patent for which an extension is being sought, including the entire specification (including claims) and drawings;

A full copy of U.S. Patent No. 6,783,965, for which extension is being sought, is attached as **Exhibit 5**.

(8) A copy of any disclaimer, certificate of correction, receipt of maintenance fee payment, or reexamination certificate issued in the patent;

A copy of a Terminal Disclaimer dated December 4, 2003 is attached as **Exhibit 6**. A copy of a Terminal Disclaimer dated August 5, 2008 is attached as **Exhibit 7**. A copy of a Certificate of Correction dated December 19, 2006 is attached as **Exhibit 8**. A copy of a Certificate of Correction dated September 1, 2009 is attached as **Exhibit 9**. A statement showing maintenance fee payment for pay year 04 is attached as **Exhibit 10**. Maintenance fee payments for pay years 08 and 12 are not yet due.

(9) **A statement that the patent claims the approved product, or a method of using or manufacturing the approved product, and a showing which lists each applicable patent claim and demonstrates the manner in which at least one such patent claim reads on the approved product, or a method of using or manufacturing the approved product:**

Claims 1, 4, 6, 7, 16, 17, 18, 19, 20, 21, 22, 24, 26, 28, 29 and 30 of the '965 Patent read on the approved product as detailed below.

Claim	Demonstration
1. Purified urate oxidase (uricase) that contains no more than about 2% of aggregates larger than octamers, wherein greater than about 20% of said uricase is in the tetrameric or octameric form.	KRYSTEXXA™ contains purified urate oxidase (uricase) that has no more than about 2% of aggregates larger than octamers, wherein greater than about 20% of said uricase is in the tetrameric or octameric form.
4. The uricase of claim 1, wherein the uricase is recombinant.	KRYSTEXXA™ contains recombinant uricase.
6. The uricase of claim 4, wherein the uricase is chimeric.	KRYSTEXXA™ contains chimeric uricase.
7. The uricase of claim 6, wherein the chimeric uricase contains portions of porcine liver and baboon liver uricase.	KRYSTEXXA™ contains chimeric uricase containing portions of porcine liver and baboon liver uricase.
16. A uricase conjugate comprising the uricase of claim 1 conjugated to poly(ethylene glycol) or poly(ethylene oxide).	KRYSTEXXA™ contains purified urate oxidase (uricase) conjugated to poly(ethylene glycol).
17. The uricase conjugate of claim 16, wherein said poly(ethylene glycol) is monomethoxy poly(ethylene glycol).	KRYSTEXXA™ contains purified urate oxidase (uricase) conjugated to monomethoxy poly(ethylene glycol).
18. The uricase conjugate of claim 16, wherein said uricase is conjugated to said poly(ethylene glycol) or poly(ethylene oxide) via a linkage selected from the group consisting of urethane (carbamate), secondary amine and amide.	KRYSTEXXA™ contains purified urate oxidase (uricase) conjugated to poly(ethylene glycol) via a urethane (carbamate) linkage.
19. The uricase conjugate of claim 16, wherein said poly(ethylene glycol) or poly(ethylene oxide) has a molecular weight between about 5 kDa and 30 kDa.	KRYSTEXXA™ contains purified urate oxidase (uricase) conjugated to poly(ethylene glycol) of molecular weight between about 5 kDa and 30 kDa.
20. The uricase conjugate of claim 19, wherein said poly(ethylene glycol) or poly(ethylene oxide) has a molecular weight between about 10 kDa and 20 kDa.	KRYSTEXXA™ contains purified urate oxidase (uricase) conjugated to poly(ethylene glycol) of molecular weight between about 10 kDa and 20 kDa.
21. The uricase conjugate of claim 16, wherein the average number of strands of said poly(ethylene glycol) or poly(ethylene oxide) is between about 2 and 12 per uricase subunit.	KRYSTEXXA™ contains purified urate oxidase (uricase) conjugated to between an average of about 2 and 12 strands of poly(ethylene glycol) per uricase subunit.

22. The uricase conjugate of claim 21, wherein the average number of strands of said poly(ethylene glycol) or poly(ethylene oxide) is between about 6 and 10 per uricase subunit.	KRYSTEXXA™ contains purified urate oxidase (uricase) conjugated to between an average of about 6 and 10 strands of poly(ethylene glycol) per uricase subunit.
24. The uricase conjugate of claim 16, wherein the poly(ethylene glycol) or poly(ethylene oxide) is linear.	KRYSTEXXA™ contains purified urate oxidase (uricase) conjugated to linear poly(ethylene glycol).
26. A pharmaceutical composition for lowering uric acid levels in a body fluid or tissue, comprising the conjugate of claim 16 and a pharmaceutically acceptable carrier.	KRYSTEXXA™ is a pharmaceutical solution containing purified urate oxidase (uricase) conjugated to poly(ethylene glycol). KRYSTEXXA™ is approved for administration by intravenous infusion for the treatment of chronic gout in adult patients refractory to conventional therapy. See Approved Label attached as **Exhibit 3**. KRYSTEXXA™ treats chronic gout by lowering uric acid levels in a body fluid or tissue.
28. A purified fragment of uricase that contains no more than about 2% of aggregates larger than octamers, wherein said fragment is a recombinant uricase that has been truncated at the amino terminus, at the carboxyl terminus, or at both the amino and carboxyl termini, and wherein greater than about 20% of said truncated uricase is in the tetrameric or octameric form.	KRYSTEXXA™ contains purified, recombinant urate oxidase (uricase) that has been truncated at the amino terminus. Greater than about 20% of the purified uricase in KRYSTEXXA™ is in the tetrameric or octameric form and it has no more than about 2% of aggregates larger than octamers.
29. The purified uricase of claim 1, wherein about 98% to about 100% of said uricase is in the tetrameric or octameric form.	KRYSTEXXA™ contains purified urate oxidase (uricase) that is about 98% to about 100% in the tetrameric or octameric form.
30. Isolated uricase prepared by a method comprising separating uricase aggregates larger than octamers from uricase tetramers and octamers and excluding such aggregates from the isolated uricase, wherein about 98% to about 100% of said uricase is in the tetrameric or octameric form.	KRYSTEXXA™ contains isolated uricase prepared by a method comprising separating uricase aggregates larger than octamers from uricase tetramers and octamers and excluding such aggregates from the isolated uricase. KRYSTEXXA™ contains isolated uricase that is about 98% to about 100% in the tetrameric or octameric form.

(10) A statement beginning on a new page of the relevant dates and information pursuant to 35 U.S.C. 156(g) in order to enable the Secretary of Health and Human Services or the Secretary of Agriculture, as appropriate, to determine the applicable regulatory review period as follows:

(i) For a patent claiming a human drug, antibiotic, or human biological product:

(A) The effective date of the investigational new drug (IND) application and the IND number;

The first IND application for the approved product was submitted to the FDA by Bio-Technology General Corporation (the predecessor of Savient Pharmaceuticals, Inc., which is the exclusive licensee of the '965 Patent) on November 15, 2001. By letter dated November 30, 2001, the FDA acknowledged receipt of the IND application on November 19, 2001, and assigned IND number BB-IND 10122, resulting in an IND effective date of December 19, 2001. A copy of the FDA acknowledgement letter is attached as **Exhibit 11**.

Under these circumstances, the "regulatory review period" under 35 U.S.C. § 156(g)(1) began on **December 19, 2001**, the effective date of BB-IND 10122.

(B) The date on which a new drug application (NDA) or a Product License Application (PLA) was initially submitted and the NDA or PLA number; and

The BLA for KRYSTEXXA™ was initially submitted by Savient Pharmaceuticals, Inc. to the FDA on October 31, 2008. By letter dated November 12, 2008, the FDA acknowledged receipt of the BLA on October 31, 2008, and assigned Submission Tracking Number (STN): BLA 125293, as confirmed by **Exhibit 12**. This establishes **October 31, 2008** as the initial submission date of the BLA for the approved product for purposes of 35 U.S.C. § 156(g)(1).

(C) The date on which the NDA was approved or the Product License issued;

The BLA for KRYSTEXXA™ was approved by the FDA approval letter dated and sent September 14, 2010, setting the effective date of the approval as the September 14, 2010 date of the letter. A copy of this FDA approval letter is attached as **Exhibit 4**. This establishes the end of the "regulatory review period" under 35 U.S.C. 156(g)(1) as **September 14, 2010**.

(11) A brief description beginning on a new page of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities;

A listing of the significant activities undertaken by the marketing applicant, and their respective dates, with respect to the approved product during the applicable regulatory review period of BB-IND 10122 and BLA 125293 is attached as **Exhibit 13**, the disclosure of which is incorporated herein in its entirety.

(12) **A statement beginning on a new page that in the opinion of the applicant the patent is eligible for the extension and a statement as to the length of extension claimed, including how the length of extension was determined;**

Statement That the Patent Is Eligible For Extension

Applicants are of the opinion that U.S. Patent No. 6,783,965 is eligible for extension under 35 U.S.C. § 156(a) because it satisfies all of the requirements for such extension as follows:

(1) 35 U.S.C. 156(a)

U.S. Patent No. 6,783,965 claims the approved product as detailed in Section (9) above.

(2) 35 U.S.C. 156 (a)(l)

U.S. Patent No. 6,783,965 was granted on August 31, 2004 on an earliest filed U.S. application filed on February 10, 2000. A terminal disclaimer was filed with regard to U.S. Patent No. 6,576,235, which application was filed on August 6, 1999, with no terminal disclaimers. As such, the patent expires on August 6, 2019, being 20 years from filing of U.S. Patent No. 6,576,235. This application, therefore, has been submitted before the expiration of the patent term of the '965 Patent.

(3) 35 U.S.C. 156(a)(2)

The term of the '965 Patent has never been extended.

(4) 35 U.S.C. 156(a)(3)

This application is being submitted by the owners of record of U.S. Patent No. 6,783,965 through an assignment from the inventors as detailed on pages 1-2 above and in **Exhibit 1**, in accordance with the requirement of 35 U.S.C. 156(d) and rules of the U.S. Patent and Trademark Office.

(5) 35 U.S.C. 156(a)(4)

As evidenced by the September 14, 2010 approval letter from the FDA (**Exhibit 4**), KRYSTEXXA™ was subject to a regulatory review period under Section 351 of the Public Health Service Act (42 U.S.C. § 262) before its commercial marketing or use.

(6) 35 U.S.C. 156(a)(5)(A)

The permission for commercial marketing of KRYSTEXXA™ after this regulatory review period is the first permitted commercial marketing of the approved product or any active ingredient thereof, under provision of the Public Health Service Act (42 U.S.C. § 262) under which the regulatory review period occurred, as confirmed by the absence of any approved BLA for the approved product or any active ingredient thereof prior to September 14, 2010.

(7) 35 U.S.C. 156(a)(5)(B)

No other patent has been extended for the same regulatory review period for the product KRYSTEXXA™.

Statement Regarding Length of Extension Claimed

The term of U.S. Patent 6,783,965 should be extended **1445 days** from August 6, 2019 to **July 21, 2023**. In accordance with the implementing regulations of 37 C.F.R. 1.775 with respect to patent term extensions for a human drug product, the term extension of U.S. Patent No. 6,783,965 based on the regulatory review of KRYSTEXXA™ was determined as follows:

> **Section 1.775 Calculation of patent term extension for a human drug, antibiotic drug or human biological product.**
>
> **(a) If a determination is made pursuant to §1.750 that a patent for a human drug, antibiotic drug or human biological product is eligible for extension, the term shall be extended by the time as calculated in days in the manner indicated by this section. The patent term extension will run from**

the original expiration date of the patent or any earlier date set by terminal disclaimer (§1.321).

U.S. Patent No. 6,783,965 issued on August 31, 2004 from an earlier filed U.S. application filed on February 10, 2000. A terminal disclaimer was filed with regard to U.S. Patent No. 6,576,235, application for which was filed on August 6, 1999, with no terminal disclaimers. Pursuant to 35 U.S.C. 154(a)(2), this patent is entitled to an original term of 20 years from filing of the application for U.S. Patent No. 6,576,235 on August 6, 1999, which provides an original expiration date of August 6, 2019.

(b) The term of the patent for a human drug, antibiotic drug or human biological product will be extended by the length of the regulatory review period for the product as determined by the Secretary of Health and Human Services, reduced as appropriate pursuant to paragraphs (d)(1) through (d)(6) of this section.

(c) The length of the regulatory review period for a human drug, antibiotic drug or human biological product will be determined by the Secretary of Health and Human Services. Under 35 U.S.C. 156(g)(1)(B), it is the sum of —

(1) The number of days in the period beginning on the date an exemption under subsection (i) of section 505 or subsection (d) of section 507 of the Federal Food, Drug, and Cosmetic Act became effective for the approved product and ending on the date the application was initially submitted for such product under those sections or under section 351 of the Public Health Service Act; and

(2) The number of days in the period beginning on the date the application was initially submitted for the approved product under section 351 of the Public Health Service Act, subsection (b) of section 505 or section 507 of the Federal Food, Drug, and Cosmetic Act and ending on the date such application was approved under such section.

The number of days in the IND testing period of paragraph (c)(1) extends from the effective date of BB-IND 10122 on December 19, 2001 to the filing (receipt) of STN:BLA 125293 on October 31, 2008, being **2509 days**.

The number of days in the NDA approval period of paragraph (c)(2) extends from the filing of STN:BLA 125293 on October 31, 2008 to the date of approval of STN:BLA 125293 on September 14, 2010, being **684 days**.

The regulatory review period is the sum of the periods of paragraphs (c)(1) and (c)(2), being **3193 days**.

> **(d) The term of the patent as extended for a human drug, antibiotic drug or human biological product will be determined by —**
>
> **(1) Subtracting from the number of days determined by the Secretary of Health and Human Services to be in the regulatory review period:**
>
> **(i) The number of days in the periods of paragraphs (c)(1) and (c)(2) of this section which were on and before the date on which the patent issued;**
>
> **(ii) The number of days in the periods of paragraphs (c)(1) and (c)(2) of this section during which it is determined under 35 U.S.C. 156(d)(2)(B) by the Secretary of Health and Human Services that applicant did not act with due diligence;**
>
> **(iii) One-half the number of days remaining in the period defined by paragraph (c)(1) of this section after that period is reduced in accordance with paragraphs (d)(1) (i) and (ii) of this section; half days will be ignored for purposes of subtraction;**

With respect to paragraph (d)(1)(i), the number of days in the periods of paragraphs (c)(1) and (c)(2) on and before August 31, 2004 on which U.S. Patent No. 6,783,965 issued is from the effective date of BB-IND 10122 on December 19, 2001 to the issue of U.S. Patent No. 6,783,965 on August 31, 2004, being **987 days**.

With respect to paragraph (d)(1)(ii), 35 U.S.C. 156 (d)(2)(B) provides that if a petition is submitted to the Secretary not later than 180 days after publication of the determination of the applicable regulatory review period, upon which it may reasonably be determined that the applicant did not act with due diligence during the applicable regulatory review period, the Secretary shall determine if the applicant acted with due diligence during the

applicable regulatory review period. The Secretary making this determination shall notify the Director of the determination and shall publish in the Federal register a notice of such determination together with the factual and legal basis for such determination. Any interested person may request, within the 60-day period beginning on the publication of a determination, the Secretary to hold an informal hearing on the determination. If such request is made within such period, the Secretary shall hold such hearing, and shall provide notice of the hearing to the owner of the patent involved and to any interested person and provide the owner and any interested person an opportunity to participate in the hearing. Within 30 days after the completion of the hearing, the secretary shall affirm or revise the determination which was the subject of the hearing and shall notify the Director of any revision of the determination and shall publish any such revision in the Federal Register. There has been no such petition or determination by the Secretary, and thus the number of days under (d)(1)(ii) is **0 (zero) days**.

With respect to paragraph (d)(1)(iii), one-half the number of days remaining in the period defined by paragraph (c)(1) – **2509 days** – after that period is reduced in accordance with paragraphs (d)(1) (i) – **987 days** – and (d)(1) (ii) – **0 days** – is **761 days**, ignoring the half day.

Subtracting from the regulatory review period of **3193 days** as determined above pursuant to section 1.775(c) the number of days determined above with respect to sections 1.775(d)(1)(i), (ii) and (iii), the term of patent extension *for U.S. Patent No. 6,783,965* is **3193 days** minus **987 days** minus **0 (zero) days** minus **761 days** for a sum total of **1445 days**.

(2) By adding the number of days determined in paragraph (d)(1) of this section to the original term of the patent as shortened by any terminal disclaimer;

The original expiration date of U.S. Patent No. 6,783,965 is August 6, 2019 after being shortened by terminal disclaimer. Adding the **1445 days** determined in sections 1.775(d)(1) to the original term of the patent results in an extended term to **July 21, 2023**.

(3) By adding 14 years to the date of approval of the application under section 351 of the Public Health Service Act, or subsection (b) of section 505 or section 507 of the Federal Food, Drug, and Cosmetic Act;

Adding 14 years to the September 14, 2010 date of approval of the BLA results in the date September 14, 2024.

(4) By comparing the dates for the ends of the periods obtained pursuant to paragraphs (d)(2) and (d)(3) of this section with each other and selecting the earlier date;

The earlier date of **July 21, 2023** and September 14, 2024 is **July 21, 2023**.

(5) If the original patent was issued after September 24, 1984,

(i) By adding 5 years to the original expiration date of the patent or any earlier date set by terminal disclaimer; and

(ii) By comparing the dates obtained pursuant to paragraphs (d)(4) and (d)(5)(i) of this section with each other and selecting the earlier date;

Adding 5 years to the original expiration date of the patent of August 6, 2019 gives a date of August 6, 2024. The earlier date of **July 21, 2023** and August 6, 2024 is **July 21, 2023**.

Thus, as calculated above, the term of U.S. Patent No. 6,783,965 is eligible for a **1445 days** extension to **July 21, 2023.**

(13) **A statement that applicant acknowledges a duty to disclose to the Director of the United States Patent and Trademark Office and the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to the determination of entitlement to the extension sought (see §1.765);**

Applicants acknowledge a duty to disclose to the Director of the United States Patent and Trademark Office and the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to the determination of entitlement to the extension sought.

(14) The prescribed fee for receiving and acting upon the application for extension (see §1.20(j)); and

The Patent and Trademark Office is authorized to charge the filing fee of $1,120.00 and any additional fees which may be required by this or any other related paper, or to credit any overpayment to Deposit Account No. 19-0036.

(15) The name, address, and telephone number of the person to whom inquiries and correspondence relating to the application for patent term extension are to be directed.

Eldora Ellison Floyd, Reg. No. 39,967
Helene C. Carlson, Reg. No. 47,473
Sterne, Kessler, Goldstein & Fox, PLLC
1100 New York Avenue, NW
Washington, DC 20005
(202) 371-2600

FOR: Mountain View Pharmaceuticals, Inc.
SIGNATURE: _____
BY: Mark G.P. Saifer, Ph.D.
TITLE: Vice President and Scientific Director
DATE: _____

FOR: Duke University
SIGNATURE: _____
BY: Robert L. Taber, Ph.D.
TITLE: Vice Chancellor, Corporate and Venture Development
DATE: 11-8-10

EXHIBIT 1

Client Code: MVIEW.005A

MM 5.22.00 RE 06-12-2000 :T

101378676

TO THE ASSISTANT COMMISSIONER FOR ...ocuments or copy thereof.

1. Name of conveying party(ies): (If multiple a... numerically)

Merry R. Sherman, Ph.D., Mark G.P. Saifer, Ph.D., and L. David Williams, Ph.D.

Additional name(s) of conveying party(ies) attached?
( ) Yes (X) No

... of receiving party(ies):

Name: Mountain View Pharmaceuticals, Inc.
Internal Address:
Street Address: 3475 S-Edison Way
City: Menlo Park **State:** CA **ZIP:** 94025

Additional name(s) of receiving party(ies) attached?
( ) Yes (X) No

3. Nature of conveyance:

(X) Assignment
( ) Merger
( ) Security Agreement
( ) Change of Name
( ) Other:

Execution Date: (If multiple assignors, list execution dates in numerical order corresponding to numbers indicated in 1 above) 1) April 26, 2000, 2) April 26, 2000 and 3) April 26, 2000

4. Application number(s) or Patent number(s):

( ) Application(s) filed herewith Execution Date(s):

(X) Patent Application No.: 09/501,730
Filing Date: February 10, 2000

( ) Patent No.:
Issue Date:

Additional numbers attached? ( ) Yes (X) No

5. Name and address of party to whom correspondence concerning document should be mailed:

Name: Dale C. Hunt
KNOBBE, MARTENS, OLSON & BEAR, LLP
Customer No. 20,995
Internal Address: Sixteenth Floor
Street Address: 620 Newport Center Drive
City: Newport Beach **State:** CA **ZIP:** 92660
Attorney's Docket No.: MVIEW.005A

7. Total fee (37 CFR 3.41): $40

(X) Enclosed
(X) Authorized to be charged to deposit account if any additional fees are required, or to credit any overpayment

8. Deposit account number: 11-1410

Please charge this account for any additional fees which may be required, or credit any overpayment to this account.

6. Total number of applications and patents involved: 1

9. Statement and signature.

To the best of my knowledge and belief, the foregoing information is true and correct, and any attached copy is a true copy of the original document.

Dale C. Hunt
Name of Person Signing

Signature

19 May 2000
Date

41,857
Registration No.

Total number of pages including cover sheet, attachments and document: 3

Mail documents to be recorded with required cover sheet information to:

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Assistant Commissioner for Patents
Box Assignments
Washington, D.C. 20231

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ASSIGNMENT

WHEREAS, We, Merry R. Sherman, Ph.D., a United States citizen, residing at 1114 Royal Lane, San Carlos, CA 94070; Mark G.P. Saifer, Ph.D., a United States citizen, residing at 1114 Royal Lane, San Carlos, CA 94070; and L. David Williams, Ph.D., a United States citizen, residing at 37709 Arlene Court, Fremont, CA 94536, have invented certain new and useful improvements in a AGGREGATE-FREE URATE OXIDASE FOR PREPARATION OF NON-IMMUNOGENIC POLYMER CONJUGATES for which we have filed an application for Letters Patent in the United States, 09/501,730, February 10, 2000;

AND WHEREAS, Mountain View Pharmaceuticals, Inc. (hereinafter "ASSIGNEE"), a California Corporation, with its principal place of business at 3475-S Edison Way, Menlo Park, California 94025, desires to acquire the entire right, title, and interest in and to the said improvements and the said Application:

NOW, THEREFORE, in consideration of the sum of One Dollar ($1.00) to me in hand paid, and other good and valuable consideration, the receipt of which is hereby acknowledged, we, the said inventors, do hereby acknowledge that we have sold, assigned, transferred and set over, and by these presents do hereby sell, assign, transfer and set over, unto the said ASSIGNEE, its successors, legal representatives and assigns, the entire right, title, and interest throughout the world in, to and under the said improvements, and the said application and all divisions, renewals and continuations thereof, and all Letters Patent of the United States which may be granted thereon and all reissues and extensions thereof, and all rights of priority under International Conventions and applications for Letters Patent which may hereafter be filed for said improvements in any country or countries foreign to the United States, and all Letters Patent which may be granted for said improvements in any country or countries foreign to the United States and all extensions, renewals and reissues thereof; and we hereby authorize and request the Commissioner of Patents of the United States, and any Official of any country or countries foreign to the United States, whose duty it is to issue patents on applications as aforesaid, to issue all Letters Patent for said improvements to the said ASSIGNEE, its successors, legal representatives and assigns, in accordance with the terms of this instrument.

AND WE HEREBY covenant and agree that we will communicate to the said ASSIGNEE, successors, legal representatives and assigns, any facts known to us respecting said improvements, and testify in any legal proceeding, sign all lawful papers, execute all divisional, continuing and reissue applications, make all rightful oaths and generally do everything possible to aid the said ASSIGNEE, its successors, legal representatives and assigns, to obtain and enforce proper patent protection for said improvements in all countries.

IN TESTIMONY WHEREOF, I hereunto set my hand and seal this 26th day of April, 2000

Merry R. Sherman

Merry R. Sherman, Ph.D.

STATE OF CALIFORNIA]
COUNTY OF SAN MATEO] ss.

On 4-26-2000 before me, MICHAEL MURPHY personally appeared Merry R. Sherman, Ph.D. personally known to me (or proved to me on the basis of satisfactory evidence) to be the person(s) whose name(s) is/are subscribed to the within instrument, and acknowledged to me that she executed the same in her authorized capacity(ies), and that by her signature(s) on the instrument the person(s), or the entity upon behalf of which the person(s) acted, executed the instrument.

WITNESS my hand and official seal.

[SEAL]

MICHAEL MURPHY
COMM. #1149158
NOTARY PUBLIC - CALIFORNIA
SAN MATEO COUNTY
My Comm. Expires July 29, 2001

Michael Murphy

Notary Signature

IN TESTIMONY WHEREOF, I hereunto set my hand and seal this 26 day of April, 2000

Mark G. P. Saifer, Ph.D.

STATE OF CALIFORNIA
COUNTY OF SAN MATEO] ss.

On 4/26/2000, before me, MICHAEL MURPHY, personally appeared Mark G. P. Saifer, Ph.D., personally known to me (or proved to me on the basis of satisfactory evidence) to be the person(s) whose name(s) is/are subscribed to the within instrument, and acknowledged to me that he executed the same in his authorized capacity(ies), and that by his signature(s) on the instrument the person(s), or the entity upon behalf of which the person(s) acted, executed the instrument.

WITNESS my hand and official seal.

[SEAL] MICHAEL MURPHY COMM. #1149158 NOTARY PUBLIC • CALIFORNIA SAN MATEO COUNTY My Comm. Expires July 29, 2001

Michael Murphy
Notary Signature

IN TESTIMONY WHEREOF, I hereunto set my hand and seal this 26 day of April, 2000

L. David Williams, Ph.D.

STATE OF CALIFORNIA
COUNTY OF SAN MATEO] ss.

On 4/26/2000, before me, MICHAEL MURPHY, personally appeared L. David Williams personally known to me (or proved to me on the basis of satisfactory evidence) to be the person(s) whose name(s) is/are subscribed to the within instrument, and acknowledged to me that he executed the same in his authorized capacity(ies), and that by his signature(s) on the instrument the person(s), or the entity upon behalf of which the person(s) acted, executed the instrument.

WITNESS my hand and official seal.

[SEAL] MICHAEL MURPHY COMM. #1149158 NOTARY PUBLIC • CALIFORNIA SAN MATEO COUNTY My Comm. Expires July 29, 2001

Michael Murphy
Notary Signature

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PATENT ASSIGNMENT

Electronic Version v1.1
Stylesheet Version v1.1

SUBMISSION TYPE:	NEW ASSIGNMENT
NATURE OF CONVEYANCE:	ASSIGNMENT

CONVEYING PARTY DATA

Name	Execution Date
Michael S. HERSHFIELD	05/16/2006
Susan J. KELLY	05/17/2006

RECEIVING PARTY DATA

Name:	Duke University
Street Address:	Erwin Road
City:	Durham
State/Country:	NORTH CAROLINA
Postal Code:	27710

PROPERTY NUMBERS Total: 1

Property Type	Number
Patent Number:	6783965

OP $40.00 6783965

CORRESPONDENCE DATA

Fax Number: (202)371-2540
Correspondence will be sent via US Mail when the fax attempt is unsuccessful.
Phone: 202-371-2600
Email: jking@skgf.com
Correspondent Name: Sterne, Kessler, Goldstein & Fox PLLC
Address Line 1: 1100 New York Avenue NW
Address Line 4: Washington, DISTRICT OF COLUMBIA 20005

ATTORNEY DOCKET NUMBER:	2057.0080000/BJD/SAC
NAME OF SUBMITTER:	Shannon A. Carroll

Total Attachments: 2
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ASSIGNMENT

In consideration of the sum of One Dollar ($1.00) or equivalent and other good and valuable consideration paid to each of the undersigned inventors: **Michael S. HERSHFIELD** and **Susan J. KELLY**, hereby sell and assign to **Duke University**, a corporation formed under the laws of North Carolina, whose mailing address is Erwin Road, Durham, NC 27710 (hereafter referred to as the Assignee), his/her entire right, title and interest, including the right to sue for past infringement and to collect for all past, present and future damages, for the United States of America (as defined in 35 U.S.C. § 100) and throughout the world,

(a) in the invention known as **Aggregate-Free Urate Oxidase for Preparation of Non-Immunogenic Polymer Conjugates** for which an application for patent in the United States of America was filed on February 10, 2000 (also known as United States Application No. 09/501,730, now U.S. Patent No. 6,783,965), in any and all applications thereon, in any and all Letters Patent(s) therefor, and

(b) in any and all applications that claim the benefit of the patent application listed above in part (a), including non-provisional applications, continuing (continuation, divisional, or continuation-in-part) applications, reissues, extensions, renewals and reexaminations of the patent application or Letters Patent therefor listed above in part (a), to the full extent of the term or terms for which Letters Patents issue, and

(c) in any and all inventions described in the patent application listed above in part (a), and in any and all forms of intellectual and industrial property protection derivable from such patent application, and that are derivable from any and all continuing applications, reissues, extensions, renewals and reexaminations of such patent application, including, without limitation, patents, applications, utility models, inventor's certificates, and designs together with the right to file applications therefor, and including the right to claim the same priority rights from any previously filed applications under the International Agreement for the Protection of Industrial Property, or any other international agreement, or the domestic laws of the country in which any such application is filed, as may be applicable;

all such rights, title and interest to be held and enjoyed by the above-named Assignee, its successors, legal representatives and assigns to the same extent as all such rights, title and interest would have been held and enjoyed by the Assignor had this assignment and sale not been made.

The undersigned inventors agree to execute all papers necessary in connection with the application(s) and any non-provisional, continuing (continuation, divisional, or continuation-in-part), reissue, reexamination or corresponding application(s) thereof and also to execute separate assignments in connection with such application(s) as the Assignee may deem necessary or expedient.

The undersigned inventors agree to execute all papers necessary in connection with any interference or patent enforcement action (judicial or otherwise) related to the application(s) or any non-provisional, continuing (continuation, divisional, or continuation-in-part), reissue or reexamination application(s) thereof and to cooperate with the Assignee in every way possible in obtaining evidence and going forward with such interference or patent enforcement action.

The undersigned inventors hereby represent that he/she has full right to convey the entire interest herein assigned, and that he/she has not executed, and will not execute, any agreement in conflict therewith.

The undersigned inventors hereby grant the patent practitioners associated with **CUSTOMER NUMBER 26111** the power to insert in this assignment any further identification that may be necessary or desirable in order to comply with the rules of the United States Patent and Trademark Office for recordation of this document.

IN WITNESS WHEREOF, executed by the undersigned inventors on the date opposite his/her name.

Date: 5/16/2006 Signature of Inventor: _____
Michael S. HERSHFIELD

Date: 5/17/2006 Signature of Inventor: _____
Susan J. KELLY

519762

EXHIBIT 2

SAVIENT
PHARMACEUTICALS, INC.

One Tower Center, 14th Floor
East Brunswick, NJ 08816

PHILIP K. YACHMETZ
Senior Vice President
General Counsel & Secretary

732-418-9300 Tel
732-565-4705 Direct
732-418-9065 Fax
pyachmetz@savientpharma.com

November 5, 2010

Commissioner for Patents
U.S. Patent and Trademark Office
Mail Stop Patent Ext.
Randolph Building
401 Dulany Street
Alexandria, VA 22314

To Whom It May Concern:

Pursuant to 35 U.S.C. 156(d)(1), Savient Pharmaceuticals, Inc. ("Savient") hereby authorizes Mountain View Pharmaceuticals, Inc. and Duke University (collectively, "the Applicants") to rely upon the marketing application activities of Savient before the U.S. Food and Drug Administration ("FDA") for the application for extension of patent term of the United States Patent No. 6,783,965 ("the '965 Patent").

Savient is the holder of marketing approval for KRYSTEXXA™, the approved product that is relevant to the application for extension of patent term of the '965 Patent. The first IND application for KRYSTEXXA™ was submitted to the FDA by Savient's predecessor – Bio-Technology General Corporation ("BTG") in 2001.

To Savient's knowledge, the Applicants are the owners of the '965 Patent. By an agreement effective on August 12, 1998, the Applicants provided BTG an

exclusive license to use the '965 Patent, including for the regulatory review of KRYSTEXXA™.

An agency relationship between the Applicants and Savient existed during the regulatory review period of KRYSTEXXA™.

Sincerely,

Philip K. Yachmetz
Senior Vice President
General Counsel & Secretary

EXHIBIT 3

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use KRYSTEXXA safely and effectively. See full prescribing information for KRYSTEXXA

KRYSTEXXA™ (pegloticase)
Injection, for intravenous infusion

Initial US Approval: 2010

WARNING: ANAPHYLAXIS and INFUSION REACTIONS
See full prescribing information for complete boxed warning.
- **Anaphylaxis and infusion reactions have been reported to occur during and after administration of KRYSTEXXA (5.1, 5.2).**
- **KRYSTEXXA should be administered in healthcare settings and by healthcare providers prepared to manage anaphylaxis and infusion reactions.**
- **Patients should be pre-medicated with antihistamines and corticosteroids.**
- **Patients should be closely monitored for an appropriate period of time for anaphylaxis after administration of KRYSTEXXA.**
- **Monitor serum uric acid levels prior to infusions and consider discontinuing treatment if levels increase to above 6 mg/dL, particularly when 2 consecutive levels above 6 mg/dL are observed.**

----------INDICATIONS AND USAGE----------

KRYSTEXXA™ (pegloticase) is a PEGylated uric acid specific enzyme indicated for the treatment of chronic gout in adult patients refractory to conventional therapy. (1)

Important Limitations of Use:
KRYSTEXXA is not recommended for the treatment of asymptomatic hyperuricemia. (1)

----------DOSAGE AND ADMINISTRATION----------

- For adult patients 8 mg given as an intravenous infusion every two weeks. (2.1)
- Do not administer as an intravenous push or bolus. (2.3)
- Monitor serum uric acid levels before each infusion. (2.3)
- Patients should be pre-medicated with antihistamines and corticosteroids. (2.3, 5.1, 5.2)
- Administer in a healthcare setting by healthcare providers prepared to manage anaphylaxis. (2.3, 5.1, 5.2)
- The KRYSTEXXA admixture should only be administered by intravenous infusion over no less than 120 minutes via gravity feed, syringe-type pump, or infusion pump. (2.3)

----------DOSAGE FORMS AND STRENGTHS----------

- 1 mL sterile concentrate for dilution containing 8 mg of pegloticase protein, expressed in uricase protein amounts. (3)

----------CONTRAINDICATIONS----------

- **Glucose-6-phosphate dehydrogenase (G6PD) Deficiency**: Before starting KRYSTEXXA, patients at higher risk for G6PD deficiency (e.g., those of African and Mediterranean ancestry) should be screened due to the risk of hemolysis and methemoglobinemia. (4)

----------WARNINGS AND PRECAUTIONS----------

- **Anaphylaxis:** Anaphylaxis occurred in patients treated with KRYSTEXXA. Anaphylaxis may occur with any infusion, including a first infusion, and generally manifests within 2 hours of the infusion. However, delayed-type hypersensitivity reactions have also been reported. KRYSTEXXA should be administered in healthcare settings and by healthcare providers prepared to manage anaphylaxis. Patients should be pre-medicated with antihistamines and corticosteroids. Patients should be closely monitored for an appropriate period of time for anaphylaxis after administration of KRYSTEXXA. (5.1)
- **Infusion Reactions**: Infusion reactions occurred in patients treated with KRYSTEXXA. KRYSTEXXA should be administered in a healthcare setting and by healthcare providers prepared to manage infusion reactions. Patients should be pre-medicated with antihistamines and corticosteroids. Monitor patients closely for signs and symptoms of infusion reactions. In the event of an infusion reaction, the infusion should be slowed, or stopped and restarted at a slower rate. If a severe infusion reaction occurs, discontinue infusion and institute treatment as needed. The risk of an infusion reaction is higher in patients who have lost therapeutic response. (5.2)
- **Gout Flares:** An increase in gout flares is frequently observed upon initiation of anti-hyperuricemic therapy, including treatment with KRYSTEXXA. If a gout flare occurs during treatment, KRYSTEXXA need not be discontinued. Gout flare prophylaxis (i.e., non-steroidal anti-inflammatory drugs [NSAID] or colchicine upon initiation of treatment) is recommended for at least the first 6 months of therapy unless medically contraindicated or not tolerated. (5.3)
- **Congestive Heart Failure**: KRYSTEXXA has not been formally studied in patients with congestive heart failure, but some patients in clinical trials experienced exacerbation. Exercise caution when using KRYSTEXXA in patients who have congestive heart failure and monitor patients closely following infusion. (5.4)

----------ADVERSE REACTIONS----------

The most common adverse reactions (occurring in at least 5% of KRYSTEXXA-treated patients) are gout flares, infusion reactions, nausea, contusion or ecchymosis, nasopharyngitis, constipation, chest pain, anaphylaxis and vomiting. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Savient Pharmaceuticals, Inc. at 1-888-579-7839 (1-888-KRYSTEXXA) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 09/2010

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: ANAPHYLAXIS AND INFUSION REACTIONS

- **Anaphylaxis and infusion reactions have been reported to occur during and after administration of KRYSTEXXA. [*see Warnings and Precautions (5.1, 5.2)*]**
- **Anaphylaxis may occur with any infusion, including a first infusion, and generally manifests within 2 hours of the infusion. However, delayed-type hypersensitivity reactions have also been reported.**
- **KRYSTEXXA should be administered in healthcare settings and by healthcare providers prepared to manage anaphylaxis and infusion reactions.**
- **Patients should be premedicated with antihistamines and corticosteroids.**
- **Patients should be closely monitored for an appropriate period of time for anaphylaxis after administration of KRYSTEXXA.**
- **Monitor serum uric acid levels prior to infusions and consider discontinuing treatment if levels increase to above 6 mg/dL, particularly when 2 consecutive levels above 6 mg/dL are observed.**

1 INDICATIONS AND USAGE

KRYSTEXXA™ (pegloticase) is a PEGylated uric acid specific enzyme indicated for the treatment of chronic gout in adult patients refractory to conventional therapy.

Gout refractory to conventional therapy occurs in patients who have failed to normalize serum uric acid and whose signs and symptoms are inadequately controlled with xanthine oxidase inhibitors at the maximum medically appropriate dose or for whom these drugs are contraindicated.

Important Limitations of Use:
KRYSTEXXA is not recommended for the treatment of asymptomatic hyperuricemia.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage

The recommended dose and regimen of KRYSTEXXA for adult patients is 8 mg (uricase protein) given as an intravenous infusion every two weeks.

The optimal treatment duration with KRYSTEXXA has not been established.

2.2 Preparation

Visually inspect KRYSTEXXA for particulate matter and discoloration before administration, whenever solution and container permit. Do not use vials if either is present. [*see Dosage Forms and Strengths (3)*]

Use appropriate aseptic technique. Withdraw 1 mL of KRYSTEXXA from the vial into a sterile syringe. Discard any unused portion of product remaining in the 2 mL vial. Inject into

a single 250 mL bag of 0.9% Sodium Chloride Injection, USP or 0.45% Sodium Chloride Injection, USP for intravenous infusion. Do not mix or dilute with other drugs.

Invert the infusion bag containing the dilute KRYSTEXXA solution a number of times to ensure thorough mixing. Do not shake.

KRYSTEXXA diluted in infusion bags is stable for 4 hours at 2° to 8°C (36° to 46°F) and at room temperature (20° to 25°C, 68° to 77°F). However it is recommended that diluted solutions be stored under refrigeration, not frozen, protected from light, and used within 4 hours of dilution. [*see How Supplied/Storage and Handling (16)*]

Before administration, allow the diluted solution of KRYSTEXXA to reach room temperature. KRYSTEXXA in a vial or in an intravenous infusion fluid should never be subjected to artificial heating (e.g., hot water, microwave).

2.3 Administration

Do not administer as an intravenous push or bolus.

Monitoring Therapy: The risk of anaphylaxis and infusion reactions is higher in patients who have lost therapeutic response. Monitor serum uric acid levels prior to infusions and consider discontinuing treatment if levels increase to above 6 mg/dL, particularly when 2 consecutive levels above 6 mg/dL are observed. [*see Warnings and Precautions (5.1, 5.2)*]

The KRYSTEXXA admixture should only be administered by intravenous infusion over no less than 120 minutes via gravity feed, syringe-type pump, or infusion pump.

Patients should receive pre-infusion medications (e.g. antihistamines, corticosteroids), to minimize the risk of anaphylaxis and infusion reactions. Administer KRYSTEXXA in a healthcare setting and by healthcare providers prepared to manage anaphylaxis and infusion reactions, and observe patients for an appropriate period of time after administration. [*see Warnings and Precautions (5.1, 5.2)*]

If an infusion reaction occurs during the administration of KRYSTEXXA, the infusion may be slowed, or stopped and restarted at a slower rate, at the discretion of the physician. Since infusion reactions can occur after completion of infusion, observation of patients for approximately an hour post-infusion should be considered. [*see Warnings and Precautions (5.2), Adverse Reactions (6.1)*]

3 DOSAGE FORMS AND STRENGTHS

KRYSTEXXA is a clear, colorless, sterile 8 mg/mL solution of pegloticase in a 2 mL single-use vial, expressed as amounts of uricase protein. KRYSTEXXA must be diluted prior to use.

4 CONTRAINDICATIONS

Glucose-6-phosphate dehydrogenase (G6PD) deficiency: KRYSTEXXA is contraindicated in patients with G6PD deficiency due to the risk of hemolysis and

methemoglobinemia. It is recommended that patients at higher risk for G6PD deficiency (e.g., patients of African or Mediterranean ancestry) be screened for G6PD deficiency before starting KRYSTEXXA.

5 WARNINGS AND PRECAUTIONS

5.1 Anaphylaxis

During pre-marketing controlled clinical trials, anaphylaxis was reported with a frequency of 6.5% of patients treated with KRYSTEXXA every 2 weeks, compared to none with placebo. Manifestations included wheezing, peri-oral or lingual edema, or hemodynamic instability, with or without rash or urticaria. Cases occurred in patients being pre-treated with one or more doses of an oral antihistamine, an intravenous corticosteroid and/or acetaminophen. This pre-treatment may have blunted or obscured symptoms or signs of anaphylaxis and therefore the reported frequency may be an underestimate. [*See Adverse Reactions (6)*]

KRYSTEXXA should be administered in a healthcare setting by healthcare providers prepared to manage anaphylaxis. Patients should be pre-treated with antihistamines and corticosteroids. Anaphylaxis may occur with any infusion, including a first infusion, and generally manifests within 2 hours of the infusion. However, delayed type hypersensitivity reactions have also been reported. Patients should be closely monitored for an appropriate period of time for anaphylaxis after administration of KRYSTEXXA. Patients should be informed of the symptoms and signs of anaphylaxis and instructed to seek immediate medical care should anaphylaxis occur after discharge from the healthcare setting.

The risk of anaphylaxis is higher in patients whose uric acid level increases to above 6 mg/dL, particularly when 2 consecutive levels above 6 mg/dL are observed. Monitor serum uric acid levels prior to infusions and consider discontinuing treatment if levels increase to above 6 mg/dL.

5.2 Infusion Reactions

During pre-marketing controlled clinical trials, infusion reactions were reported in 26% of patients treated with KRYSTEXXA 8 mg every 2 weeks, and 41% of patients treated with KRYSTEXXA 8 mg every 4 weeks, compared to 5% of patients treated with placebo. These infusion reactions occurred in patients being pre-treated with an oral antihistamine, intravenous corticosteroid and/or acetaminophen. This pre-treatment may have blunted or obscured symptoms or signs of infusion reactions and therefore the reported frequency may be an underestimate. [*See Adverse Reactions (6)*]

KRYSTEXXA should be administered in a healthcare setting by healthcare providers prepared to manage infusion reactions. Patients should be pre-treated with antihistamines and corticosteroids. KRYSTEXXA should be infused slowly over no less than 120 minutes. In the event of an infusion reaction, the infusion should be slowed, or stopped and restarted at a slower rate.

The risk of infusion reaction is higher in patients whose uric acid level increases to above 6 mg/dL, particularly when 2 consecutive levels above 6 mg/dL are observed. Monitor serum

uric acid levels prior to infusions and consider discontinuing treatment if levels increase to above 6 mg/dL.

5.3 Gout Flares

Gout flares may occur after initiation of KRYSTEXXA. [*see Adverse Reactions (6.1)*] An increase in gout flares is frequently observed upon initiation of anti-hyperuricemic therapy, due to changing serum uric acid levels resulting in mobilization of urate from tissue deposits. Gout flare prophylaxis with a non-steroidal anti-inflammatory drug (NSAID) or colchicine is recommended starting at least 1 week before initiation of KRYSTEXXA therapy and lasting at least 6 months, unless medically contraindicated or not tolerated. KRYSTEXXA does not need to be discontinued because of a gout flare. The gout flare should be managed concurrently as appropriate for the individual patient. [*see Dosage and Administration (2)*)]

5.4 Congestive Heart Failure

KRYSTEXXA has not been formally studied in patients with congestive heart failure, but some patients in the clinical trials experienced exacerbation. [*see Adverse Reactions (6.1)*] Exercise caution when using KRYSTEXXA in patients who have congestive heart failure and monitor patients closely following infusion.

5.5 Re-treatment with KRYSTEXXA

No controlled trial data are available on the safety and efficacy of re-treatment with KRYSTEXXA after stopping treatment for longer than 4 weeks. Due to the immunogenicity of KRYSTEXXA, patients receiving re-treatment may be at increased risk of anaphylaxis and infusion reactions. Therefore, patients receiving re-treatment after a drug-free interval should be monitored carefully. [*see Adverse Reactions (6.2)*]

6 ADVERSE REACTIONS

The most commonly reported serious adverse reactions from pre-marketing controlled clinical trials were anaphylaxis, which occurred at a frequency of 6.5% in patients treated with KRYSTEXXA 8 mg every 2 weeks, compared to none with placebo; infusion reactions, which occurred at a frequency of 26% in patients treated with KRYSTEXXA 8 mg every 2 weeks, compared to 5% treated with placebo; and gout flares, which were more common during the first 3 months of treatment with KRYSTEXXA compared with placebo. All patients in pre-marketing controlled clinical trials were pre-treated with an oral antihistamine, intravenous corticosteroid and/or acetaminophen to prevent anaphylaxis and infusion reaction. Patients also received non-steroidal anti-inflammatory drugs or colchicine, or both, for at least 7 days as gout flare prophylaxis before beginning KRYSTEXXA treatment. [*see Boxed Warning, Warnings and Precautions (5.1, 5.2, 5.3)*]

6.1 Clinical Trials Experience

The data described below reflect exposure to KRYSTEXXA in patients with chronic gout refractory to conventional therapy in two replicate randomized, placebo-controlled, double-blind 6-month clinical trials: 85 patients were treated with KRYSTEXXA 8 mg every 2 weeks; 84 patients were treated with KRYSTEXXA 8 mg every 4 weeks; and 43 patients were treated with placebo. These patients were between the ages of 23 and 89 years (average

55 years); 173 patients were male and 39 were female; and 143 patients were White/Caucasian, 27 were Black/African American, 24 were Hispanic/Latino and 18 were all other ethnicities. Common co-morbid conditions among the enrolled patients included hypertension (72%), dyslipidemia (49%), chronic kidney disease (28%), diabetes (24%), coronary artery disease (18%), arrhythmia (16%), and cardiac failure/left ventricular dysfunction (12%).

Because clinical studies are conducted under widely varying and controlled conditions, adverse reaction rates observed in clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug, and may not predict the rates observed in a broader patient population in clinical practice.

Anaphylaxis:
Diagnostic criteria of anaphylaxis were skin or mucosal tissue involvement, and, either airway compromise, and/or reduced blood pressure with or without associated symptoms, and a temporal relationship to KRYSTEXXA or placebo injection with no other identifiable cause. Using these clinical criteria, anaphylaxis was identified in 14 (5.1%) of 273 total patients studied in the clinical program of IV KRYSTEXXA. The frequency was 6.5% for the every 2-week dosing regimen (8 of 123 patients), and 4.8% for the 4-week dosing frequency (6 of 126) of KRYSTEXXA. There were no cases of anaphylaxis in patients receiving placebo. Anaphylaxis generally occurred within 2 hours after treatment. This occurred with patients being pre-treated with an oral antihistamine, intravenous corticosteroid, and acetaminophen. [see *Boxed Warning, Warnings and Precautions (5.1, 5.2)*]

Infusion Reactions:
Infusion reactions occurred in 26% of patients in the 2 week dosing regimen group and 41% of patients in the 4 week dosing regimen group, compared to 5% of placebo-treated patients. Manifestations of these reactions included urticaria (frequency of 10.6%), dyspnea (frequency of 7.1%), chest discomfort (frequency of 9.5%), chest pain (frequency of 9.5%), erythema (frequency of 9.5%), and pruritus (frequency of 9.5%). These manifestations overlap with the symptoms of anaphylaxis, but in a given patient did not occur together to satisfy the clinical criteria for diagnosing anaphylaxis. Infusion reactions are thought to result from release of various mediators, such as cytokines. Infusion reactions occurred at any time during a course of treatment with approximately 3% occurring with the first infusion, and approximately 91% occurred during the time of infusion. Some infusion reaction manifestations were reduced with slowing the rate of infusion, or stopping the infusion and restarting the infusion at a slower rate. These infusion reactions occurred with all patients being pre-treated with an oral antihistamine, intravenous corticosteroid and acetaminophen. [*see Boxed Warning, Warnings and Precautions (5.1, 5.2)*]

Gout Flares:
Gout flares were common in the study patients before randomization to treatment, with patients experiencing an average of 10 flares in the preceding 18 months prior to study entry. During the controlled treatment period with KRYSTEXXA or placebo, the frequencies of gout flares were high in all treatment groups, but more so with KRYSTEXXA treatment

during the first 3 months of treatment, which seemed to decrease in the subsequent 3 months of treatment. The percentages of patients with any flare for the first 3 months were 74%, 81%, and 51%, for KRYSTEXXA 8 mg every 2 weeks, KRYSTEXXA 8 mg every 4 weeks, and placebo, respectively. The percentages of patients with any flare for the subsequent 3 months were 41%, 57%, and 67%, for KRYSTEXXA 8 mg every 2 weeks, KRYSTEXXA 8 mg every 4 weeks, and placebo, respectively. Patients received gout flare prophylaxis with colchicine and/or nonsteroidal anti-inflammatory drugs (NSAIDs) starting at least one week before receiving KRYSTEXXA. [*see Warnings and Precautions (5.3)*]

Congestive Heart Failure:
Two cases of congestive heart failure exacerbation occurred during the trials in patients receiving treatment with KRYSTEXXA 8 mg every 2 weeks. No cases were reported in placebo-treated patients. Four subjects had exacerbations of pre-existing congestive heart failure while receiving KRYSTEXXA 8 mg every 2 weeks during the open-label extension study. [*see Warnings and Precautions (5.4)*].

Other Adverse Reactions:
The most commonly reported adverse reactions that occurred in greater than or equal to 5% of patients treated with KRYSTEXXA 8mg every 2 weeks are provided in Table 1.

Table 1. Adverse Reactions Occurring in 5% or More of Patients Treated with KRYSTEXXA Compared to Placebo

Adverse Reaction (Preferred Term)	KRYSTEXXA 8 mg every 2 weeks (N=85) N[a] (%)	Placebo (N=43) N (%)
Gout flare	65 (77%)	35 (81%)
Infusion reaction	22 (26%)	2 (5%)
Nausea	10 (12%)	1 (2%)
Contusion[b] or Ecchymosis[b]	9 (11%)	2 (5%)
Nasopharyngitis	6 (7%)	1 (2%)
Constipation	5 (6%)	2 (5%)
Chest Pain	5 (6%)	1 (2%)
Anaphylaxis	4 (5%)	0 (0%)
Vomiting	4 (5%)	1 (2%)

[a] If the same subject in a given group had more than one occurrence in the same preferred term event category, the subject was counted only once.
[b] Most did not occur on the day of infusion and could be related to other factors (e.g. concomitant medications relevant to contusion or ecchymosis, insulin dependent diabetes mellitus).

6.2 Immunogenicity

Anti-pegloticase antibodies developed in 92% of patients treated with KRYSTEXXA every 2 weeks, and 28% for placebo. Anti-PEG antibodies were also detected in 42% of patients treated with KRYSTEXXA. High anti-pegloticase antibody titer was associated with a failure

to maintain pegloticase-induced normalization of uric acid. The impact of anti-PEG antibodies on patients' responses to other PEG-containing therapeutics is unknown.

There was a higher incidence of infusion reactions in patients with high anti-pegloticase antibody titer: 53% (16 of 30) in the KRYSTEXXA every 2 weeks group compared to 6% in patients who had undetectable or low antibody titers.

As with all therapeutic proteins, there is a potential for immunogenicity. The observed incidence of antibody positivity in an assay is highly dependent on several factors including assay sensitivity and specificity and assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, the comparison of the incidence of antibodies to pegloticase with the incidence of antibodies to other products may be misleading.

7 DRUG INTERACTIONS

No studies of interactions of KRYSTEXXA with other drugs have been conducted. Because anti-pegloticase antibodies appear to bind to the PEG portion of the drug, there may be potential for binding with other PEGylated products. The impact of anti-PEG antibodies on patients' responses to other PEG-containing therapeutics is unknown.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

A complete evaluation of the reproductive and developmental toxicity of pegloticase has not been completed. Adequate animal reproduction studies have not been conducted with KRYSTEXXA. It is not known whether KRYSTEXXA can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. There are no adequate and well-controlled studies in pregnant women. KRYSTEXXA should be used during pregnancy only if clearly needed.

Pegloticase was not teratogenic in rats administered 0, 5, 10, or 40 mg/kg twice weekly by the intravenous route on gestation days 6 through 16 (the doses are approximately 6-fold to 50-fold higher than the maximum recommended human dose (MRHD) of 8 mg (0.133 mg/kg (based on a 60 kg person) every 2 weeks based on a mg/m^2 comparison).

8.3 Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, it is not recommended to administer KRYSTEXXA to a nursing mother.

8.4 Pediatric Use

The safety and effectiveness of KRYSTEXXA in pediatric patients less than 18 years of age have not been established.

8.5 Geriatric Use

Of the total number of patients treated with KRYSTEXXA 8 mg every 2 weeks in the controlled studies, 34% (29 of 85) were 65 years of age and older and 12% (10 of 85) were 75 years of age and older. No overall differences in safety or effectiveness were observed between older and younger patients, but greater sensitivity of some older individuals cannot be ruled out. No dose adjustment is needed for patients 65 years of age and older.

8.6 Renal Impairment

No dose adjustment is required for patients with renal impairment. A total of 32% (27 of 85) of patients treated with KRYSTEXXA 8 mg every 2 weeks had a creatinine clearance of ≤62.5 mL/min. No overall differences in efficacy were observed.

10 OVERDOSAGE

No reports of overdosage with KRYSTEXXA have been reported. The maximum dose that has been administered as a single intravenous dose is 12 mg as uricase protein.

Patients suspected of receiving an overdose should be monitored, and general supportive measures should be initiated as no specific antidote has been identified.

11 DESCRIPTION

KRYSTEXXA (pegloticase) is a uric acid specific enzyme which is a PEGylated product that consists of recombinant modified mammalian urate oxidase (uricase) produced by a genetically modified strain of *Escherichia coli*. Uricase is covalently conjugated to monomethoxypoly(ethylene glycol) [mPEG] (10 kDa molecular weight). The cDNA coding for uricase is based on mammalian sequences. Each uricase subunit has a molecular weight of approximately 34 kDa per subunit. The average molecular weight of pegloticase (tetrameric enzyme conjugated to mPEG) is approximately 540 kDa.

KRYSTEXXA is intended for intravenous infusion.

KRYSTEXXA is a sterile, clear, colorless solution containing 8 mg/mL pegloticase in phosphate-buffered saline.

KRYSTEXXA (pegloticase) concentrations are expressed as concentrations of uricase protein. Each mL of KRYSTEXXA contains 8 mg of uricase protein (conjugated to 24 mg of 10 kDa mPEG), 2.18 mg Disodium Hydrogen Phosphate Dihydrate ($Na_2HPO_4 \bullet 2H_2O$), 8.77 mg Sodium Chloride (NaCl), 0.43 mg Sodium Dihydrogen Phosphate Dihydrate ($NaH_2PO_4 \bullet 2H_2O$), and Water for Injection to deliver 8 mg of pegloticase (as uricase protein).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

KRYSTEXXA is a uric acid specific enzyme which is a recombinant uricase and achieves its therapeutic effect by catalyzing the oxidation of uric acid to allantoin, thereby lowering serum uric acid. Allantoin is an inert and water soluble purine metabolite. It is readily eliminated, primarily by renal excretion.

12.2 Pharmacodynamics

Approximately 24 hours following the first dose of KRYSTEXXA, mean plasma uric acid levels for subjects in the KRYSTEXXA groups were 0.7 mg/dL for the KRYSTEXXA 8 mg every 2 weeks group. In comparison, the mean plasma uric acid level for the placebo group was 8.2 mg/dL.

In a single-dose, dose-ranging trial, following 1-hour intravenous infusions of 0.5, 1, 2, 4, 8 or 12 mg of pegloticase in 24 patients with symptomatic gout (n=4 subjects/dose group), plasma uric acid decreased with increasing pegloticase dose or concentrations. The duration of suppression of plasma uric acid appeared to be positively associated with pegloticase dose. Sustained decrease in plasma uric acid below the solubility concentration of 6 mg/dL for more than 300 hours was observed with doses of 8 mg and 12 mg.

12.3 Pharmacokinetics

Pegloticase levels were determined in serum based on measurements of uricase enzyme activity.

Following single intravenous infusions of 0.5 mg to 12 mg pegloticase in 23 patients with symptomatic gout, maximum serum concentrations of pegloticase increased in proportion to the dose administered.

The population pharmacokinetic analysis showed that age, sex, weight, and creatinine clearance did not influence the pharmacokinetics of pegloticase. Significant covariates included in the model for determining clearance and volume of distribution were found to be body surface area and anti-pegloticase antibodies.

The pharmacokinetics of pegloticase has not been studied in children and adolescents.

No formal studies were conducted to examine the effects of either renal or hepatic impairment on pegloticase pharmacokinetics.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies have not been performed to evaluate the carcinogenic potential of pegloticase.

The genotoxic potential of pegloticase has not been evaluated.

Fertility studies in animals have not been performed.

13.2 Animal Toxicology and/or Pharmacology

In a 12-week intravenous repeat-dose study in dogs, there was a dose-dependent increase in vacuolated macrophages in the spleen. The presence of vacuolated macrophages likely reflects accumulated removal of injected pegloticase (foreign) material from the circulation. There was no evidence of degeneration, inflammation, or necrosis associated with the

vacuoles findings, however there was evidence of decreased functional response to liposaccharides.

In a 39-week, repeat dose dog study, there was a dose dependent increase in vacuolated cells in several organs, including the spleen, adrenal gland, liver, heart, duodenum and jejunum. In the spleen, liver, duodenum and jejunum, these vacuoles were within macrophages and most likely represented phagocytic removal of pegloticase from the circulation. However, the vacuolated cells in the heart and adrenal gland did not stain as macrophages. In the aortic outflow tract of the heart, vacuoles were in the cytoplasm of endothelial cells in the intimal lining of the aorta. In the adrenal gland, vacuoles were located within cortical cells in the zona reticularis and zona fasciculata. The clinical significance of these findings and the functional consequences are unknown.

14 CLINICAL STUDIES

The efficacy of KRYSTEXXA was studied in adult patients with chronic gout refractory to conventional therapy in two replicate, multicenter, randomized, double-blind, placebo-controlled studies of six months duration: Trial 1 and Trial 2. Patients were randomized to receive KRYSTEXXA 8 mg every 2 weeks or every 4 weeks or placebo in a 2:2:1 ratio. Studies were stratified for the presence of tophi. Seventy-one percent (71%) of patients had baseline tophi. All patients were prophylaxed with an oral antihistamine, intravenous corticosteroid and acetaminophen. Patients also received prophylaxis for gout flares with non-steroidal anti-inflammatory drugs (NSAIDs) or colchicine, or both, beginning at least one week before KRYSTEXXA treatment unless medically contraindicated or not tolerated. Patients who completed the randomized clinical trials were eligible to enroll in a 2-year open label extension study.

Entry criteria for patients to be eligible for the trials were: baseline serum uric acid (SUA) of at least 8 mg/dL; had symptomatic gout with at least 3 gout flares in the previous 18 months or at least 1 gout tophus or gouty arthritis; and had a self-reported medical contraindication to allopurinol or medical history of failure to normalize uric acid (to less than 6 mg/dL) with at least 3 months of allopurinol treatment at the maximum medically appropriate dose.

The mean age of study subjects was 55 years (23-89); 82% were male, mean body mass index (BMI) was 33 kg/m^2, mean duration of gout was 15 years, and mean baseline SUA was 10 mg/dL.

To assess the efficacy of KRYSTEXXA in lowering uric acid, the primary endpoint in both trials was the proportion of patients who achieved plasma uric acid (PUA) less than 6 mg/dL for at least 80% of the time during Month 3 and Month 6. As shown in Table 2, a greater proportion of patients treated with KRYSTEXXA every 2 weeks achieved urate lowering to below 6 mg/dL than patients receiving placebo. Although the 4 week regimen also demonstrated efficacy for the primary endpoint, this regimen was associated with increased frequency of anaphylaxis and infusion reactions and less efficacy with respect to tophi.

Table 2 Plasma Uric Acid < 6 mg/dL for at Least 80% of the Time During Months 3 and 6

Treatment Group	N	Number (%) of Subjects Who Met Response Criteria	95% Confidence Interval[1]	P-Value[2]
Trial 1				
Pegloticase 8 mg every 2 weeks	43	20 (47%)	[32%, 61%]	<0.001
Pegloticase 8 mg every 4 weeks	41	8 (20%)	[7%, 32%]	0.044
Placebo	20	0 (0%)		
Trial 2				
Pegloticase 8 mg every 2 weeks	42	16 (38%)	[23%, 53%]	<0.001
Pegloticase 8 mg every 4 weeks	43	21 (49%)	[34%, 64%]	<0.001
Placebo	23	0 (0%)		

[1] 95% confidence interval for differences in responder rate between pegloticase group vs. placebo
[2] P-value using Fisher's exact test to compare pegloticase group vs. placebo
Note: Based on post-hoc analyses of the clinical trial data, if KRYSTEXXA had been stopped when a patient's uric acid level rose to greater than 6 mg/dL on a single occasion, the incidence of infusion reactions would have been reduced by approximately 67%, but the success rates for the primary efficacy endpoint would have been reduced by approximately 20%. If KRYSTEXXA had been stopped after 2 consecutive uric acid levels greater than 6 mg/dL, the incidence of infusion reactions would have been half, and there would have been little change in the efficacy outcome.

The effect of treatment on tophi was a secondary efficacy endpoint and was assessed using standardized digital photography, image analysis, and a Central Reader blinded to treatment assignment. Approximately 70% of patients had tophi at baseline. A pooled analysis of data from Trial 1 and Trial 2 was performed as pre-specified in the protocols. At Month 6, the percentage of patients who achieved a complete response (defined as 100% resolution of at least one target tophus, no new tophi appear and no single tophus showing progression) was 45%, 26%, and 8%, with KRYSTEXXA 8 mg every 2 weeks, KRYSTEXXA 8 mg every 4 weeks, and placebo, respectively. The difference between KRYSTEXXA and placebo was statistically significant for the every 2 week dosing regimen, but not for the every 4 week dosing regimen.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

KRYSTEXXA is supplied as a clear, colorless, sterile solution in phosphate buffered saline intended for intravenous infusion after dilution. KRYSTEXXA is supplied in a single-use 2 mL glass vial with a Teflon® coated (latex-free) rubber injection stopper to deliver KRYSTEXXA as 8 mg of uricase protein in 1 mL volume.

Storage and Handling

Before the preparation for use, KRYSTEXXA must be stored in the carton and maintained at all times under refrigeration between 2° to 8°C (36° to 46°F). **Protect from light. Do not shake or freeze.**

Do not use beyond the expiration date stamped.

NDC# 54396-801-01

17 PATIENT COUNSELING INFORMATION

See Medication Guide

17.1 General Information

Provide and instruct patients to read the accompanying Medication Guide before starting treatment and before each subsequent treatment.

17.2 Anaphylaxis and Infusion Reactions

- Anaphylaxis and infusion reactions can occur at any infusion while on therapy. Counsel patients on the importance of adhering to any prescribed medications to help prevent or lessen the severity of these reactions.
- Educate patients on the signs and symptoms of anaphylaxis, including wheezing, peri-oral or lingual edema, hemodynamic instability, and rash or urticaria.
- Educate patients on the most common signs and symptoms of an infusion reaction, including urticaria (skin rash), erythema (redness of the skin), dyspnea (difficulty breathing), flushing, chest discomfort, chest pain, and rash.
- Advise patients to seek medical care immediately if they experience any symptoms of an allergic reaction during or at any time after the infusion of KRYSTEXXA. [*see Warnings and Precautions (5.1, 5.2), Adverse Reactions (6.1)*]

17.3 Glucose-6-phosphate dehydrogenase (G6PD) Deficiency

Inform patients not to take KRYSTEXXA if they have a condition known as G6PD deficiency. Explain to patients that G6PD deficiency is more frequently found in individuals of African or Mediterranean ancestry and that they may be tested to determine if they have G6PD deficiency, unless already known. [*See Contraindications (4)*]

17.4 Gout Flares

Explain to patients that gout flares may initially increase when starting treatment with KRYSTEXXA, and that medications to help reduce flares may need to be taken regularly for the first few months after KRYSTEXXA is started. [*see Warnings and Precautions (5.3), Adverse Reactions (6.1)*] Advise patients that they should not stop KRYSTEXXA therapy if they have a flare.

Manufactured by:
Savient Pharmaceuticals, Inc.
One Tower Center, 14th Floor
East Brunswick, NJ 08816

EXHIBIT 4

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Our STN: BL 125293/0

BLA APPROVAL
September 14, 2010

Savient Pharmaceuticals, Inc.
One Tower Center, 14th Floor
East Brunswick, NJ 08816

Attention: Steve Hamburger, Ph.D.
Group Vice President, Quality and Regulatory Affairs

Dear Dr. Hamburger:

Please refer to your Biologics License Application (BLA) dated and received October 31, 2008, submitted under section 351 of the Public Health Service Act for Krystexxa (pegloticase) Injection, for intravenous infusion.

We acknowledge receipt of your amendments dated November 14 and December 5, 9, 22, and 30, 2008, January 16 and 28, February 4, 6, and 27, March 10 and 19, April 3, 8, 21, 22, and 29, May 12, June 11, 18, 22, 23, 25, and 26, and July 9, 10, and 17, 2009, and March 15, April 23, June 1, 7, and 16, July 2 and 28, August 4, and September 2 (2) 3, 8(2), 9 and 14, 2010.

The March 15, 2010, submission constituted a complete response to our July 31, 2009, action letter.

We are issuing Department of Health and Human Services U.S. License No. 1801 to Savient Pharmaceuticals, East Brunswick, New Jersey, under the provisions of section 351(a) of the Public Health Service Act controlling the manufacture and sale of biological products. The license authorizes you to introduce into, or deliver for introduction into, interstate commerce those products for which your company has demonstrated compliance with establishment and product standards.

Under this license, you are authorized to manufacture the product pegloticase. Pegloticase is indicated for the treatment of chronic gout in adult patients refractory to conventional therapy.

Under this license, you are approved to manufacture pegloticase drug substance at BTG, Ltd., in Kiryat Malachi, Israel. The final formulated product will be manufactured, filled, labeled, and packaged at Enzon Pharmaceuticals, Inc., Indianapolis, Indiana. You may label your product with the proprietary name Krystexxa and market it in vials containing 32 mg of pegloticase corresponding to 8 mg uricase protein conjugated to 24 mg of 10 kDa mPEG.

The dating period for pegloticase shall be 24 months (2 years) from the date of manufacture when stored at 4° to 8°C. The date of manufacture shall be defined as the date of final sterile filtration of the formulated drug product. The dating period for your drug substance shall be 6 months when stored at 2° to 8°C. The dating period for the uricase intermediate shall be 54 days when stored at 2° to 8°C.

You are not currently required to submit samples of future lots of pegloticase to the Center for Drug Evaluation and Research (CDER) for release by the Director, CDER, under 21 CFR 610.2. We will continue to monitor compliance with 21 CFR 610.1, requiring completion of tests for conformity with standards applicable to each product prior to release of each lot.

Any changes in the manufacturing, testing, packaging, or labeling of pegloticase, or in the manufacturing facilities, will require the submission of information to your biologics license application for our review and written approval, consistent with 21 CFR 601.12.

We are approving this application for use as recommended in the enclosed agreed-upon labeling text.

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 601.14(b)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the enclosed labeling and Medication Guide. Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As* available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf. For administrative purposes, designate this submission **"Product Correspondence – Final SPL for approved BLA STN 125293/0."**

The SPL will be accessible via publicly available labeling repositories.

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

CARTON AND IMMEDIATE-CONTAINER LABELS

Submit final printed carton and immediate-container labels that are identical to the enclosed carton and container labels as soon as they are available, but no more than 30 days after they are printed. Submit these labels electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications*

and Related Submissions Using the eCTD Specifications. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Product Correspondence – Final Printed Carton and Container Labels for approved BLA STN 125293/0.**" Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with final printed labeling (FPL) that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product has an orphan drug designation for this indication, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess known serious risks of severe infusion reactions, anaphylaxis, and immune complex-related adverse events, as well as to identify unexpected risks related to fertility, pre-, peri-, and post-natal development, and cytoplasmic vacuoles in the adrenal gland and the aortic outflow tract of the heart.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

1. An observational safety study enrolling 500 patients treated with Krystexxa (pegloticase) for one year duration. Patients enrolled should have hyperuricemia and gout and be refractory to standard uric acid-lowering therapies (e.g., allopurinol). The study should include the following objectives:

a. An evaluation of the frequency and severity of infusion reactions, anaphylaxis, and immune complex-related adverse events.

b. Identification of serious adverse events associated with Krystexxa (pegloticase) therapy.

The timetable you submitted on September 14, 2010, states that you will conduct this study according to the following schedule:

Final Protocol Submission: February 2011
Study Completion Date: July 2015
Final Report Submission: December 2015

2. Conduct a male and female fertility study in rats per ICH-S5A and ICH-S5B.

The timetable you submitted on September 14, 2010, states that you will conduct this study according to the following schedule:

Final Protocol Submission: January 2011
Study Completion Date: November 2011
Final Report Submission: June 2012

3. Conduct an embryo-fetal development study in the rabbit model (Segment 2) according to ICH-S5A guidance.

The timetable you submitted on September 14, 2010, states that you will conduct this study according to the following schedule:

Final Protocol Submission (Main Study): September 2011
Study Completion (Main Study): March 2012
Final Report Submission (Main Study): September 2012

4. Conduct a peri-natal and post-natal development study in the rat model (Segment 3)

The timetable you submitted on September 14, 2010, states that you will conduct this study according to the following schedule:

Final Protocol Submission: January 2011
Study Completion: February 2012
Final Report Submission: October 2012

5. Conduct an 18-month study in dogs to evaluate the impact of cytoplasmic vacuoles in the adrenal gland and the aortic outflow tract of the heart.

The timetable you submitted on September 14, 2010, states that you will conduct this study according to the following schedule:

Final Protocol Submission: May 2011
Study Completion Date: November 2012
Final Report Submission: July 2013

6. The current anti-PEG antibody ELISA shows a very high degree of intra-and inter-assay variability possibly related to the PEG coating of the ELISA plate. This indicates either that the assay is not sufficiently optimized or that the format is unsuitable. Redevelop the anti-PEG antibody assay to address these concerns.

   Final Report Submission: April 2011

7. The sensitivity of your IgE assay, as currently designed, is insufficient to detect IgE antibodies to the product. For an antigen-specific IgE assay to be useful, it should have sensitivity in the nanogram to sub-nanogram range, and there are technologies currently available that can meet this criterion. Develop a more sensitive antigen-specific IgE assay. Consider using ECL technology.

   Final Report Submission: October 2012

8. Your IgE assay was not properly validated due to a lack of positive control antibody. Develop a suitable positive control for the IgE ELISA. Cross-linking the current rabbit polyclonal to a human IgE may be an option.

   Final Report Submission: January 2012

Submit the protocols to your IND 010122, with a cross-reference letter to this BLA 125293. Submit all final reports to your BLA 125293. Prominently identify the submissions with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

- **REQUIRED POSTMARKETING PROTOCOL UNDER 505(o)**
- **REQUIRED POSTMARKETING FINAL REPORT UNDER 505(o)**
- **REQUIRED POSTMARKETING CORRESPONDENCE UNDER 505(o)**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 601.70, requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 601.70 to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 601.70. We remind you that to comply with

505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments in your submission dated September 14, 2010. These commitments are listed below.

9. Revise the acceptance criteria for the peptide map assay used to quantify Krystexxa lysine site occupancy with PEG molecules, to specify a numerical range for all the polypeptides identified. Submit the new acceptance criteria for the assay.

   Final Report Submission: September 2012

10. Conduct a study to evaluate the sensitivity of the LC-MS Peptide Mapping Assay to detect over- and under-pegylated uricase molecules and submit the results.

    Final Report Submission: January 2011

11. Reevaluate the release criteria for the following assays. Submit the revised acceptance criteria and supporting data for the drug substance and drug product after 30 lots of Krystexxa (pegloticase) are manufactured.

    a. Enzymatic activity
    b. Km and k_{cat} determination by product accumulation and substrate depletion
    c. Monomer and HMW forms by SEC-HPLC Abs_{220}
    d. Monomer HMW and LMW forms by Abs_{214}

    Final Report Submission (for release acceptance criteria): Sept 2012

12. Reevaluate the stability acceptance criteria for the following assays. Submit the revised criteria and supporting data for the drug substance and drug product after 30 lots of Krystexxa (pegloticase) are manufactured.

    a. Enzymatic activity assay
    b. Km and k_{cat} determination by product accumulation and substrate depletion assay
    c. Monomer and HMW forms by SEC-HPLC Abs_{220} assay
    d. Monomer HMW and LMW forms by Abs_{214} assay.

    Final Report Submission (for stability acceptance criteria): June 2013

13. Develop and implement an enzymatic assay, based on product accumulation that determines K_m and k_{cat} values for release of uricase intermediate and submit the new specification and supporting data.

Validation Report Completion: June 2011
Final Report Submission (Acceptance Criteria): December 2012

14. Include stress conditions in the annual stability program for drug substance and drug product. Submit the revised stability protocols.

Final Protocol Submission: January 2011

15. Evaluate in-use stability of the drug product by assessing the impact dilution of 1.0 mL drug product (pH 7.0) into 250 mL saline solution with the worst case scenario pH (4.5) has on the final pH of the infusion solution. Submit the results of the study and risk mitigation strategies if the final pH is below 6.2.

Study Completion Date: April 2011
Final Report Submission: July 2011

16. Provide the results of aseptic fill validation and results of stability studies on three batches of Krystexxa (pegloticase) held for at least six months to support the reduction of the drug product vial overfill to that recommended in the USP.

Final Protocol Submission: November 2010
Study Completion Date: March 2011
Final Report Submission: January 2012

Submit clinical protocols to your IND 010122 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final reports to this BLA 125293. In addition, under 21 CFR 601.70 you should include a status summary of each commitment in your annual progress report of postmarketing studies to this BLA 125293. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol,**" "**Postmarketing Commitment Final Report,**" or "**Postmarketing Commitment Correspondence.**"

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)). The details of the REMS requirements were outlined in our complete response letter dated July 31, 2009.

Your proposed REMS, submitted on September 14, 2010, and appended to this letter, is approved. The REMS consists of a Medication Guide, a communication plan, and a timetable for submission of assessments of the REMS.

The REMS assessment plan should include but is not limited to the following:

a. An evaluation of the patients' and prescribers' understanding of the serious risks of Krystexxa (pegloticase).

b. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24.

c. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance with 21 CFR 208.24.

d. Specification of measures that would be taken to increase awareness if surveys of healthcare providers indicate that provider awareness is not adequate.

e. Summaries of adverse event reporting of infusion reactions, including an analysis of anaphylaxis, and whether appropriate therapy was instituted.

f. With regard to the communication plan:

1. The dates of product launch and the launch of the communication plan
2. The date(s) of mailing and number of recipients of the Dear Healthcare Provider letter (DHCP) and the Dear Infusion Site Medical Personnel letter (DISMP).
3. The number of mailings returned.
4. The sources of the recipient lists.
   The dates of the annual meetings attended and number of materials distributed.
5. The names of the journals that published the journal information piece and the dates of publication.

Assessments of an approved REMS must also include, under section 505-1(g)(3)(B) and (C), information on the status of any post approval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. With respect to any such post approval study, you must include the status of such study, including whether any difficulties completing the study have been encountered. With respect to any such post approval clinical trial, you must include the status of such clinical trial, including whether enrollment has begun, the number of participants enrolled, the expected completion date, whether any difficulties completing the clinical trial have been encountered, and registration information with respect to requirements under subsections (i) and (j) of section 402 of the Public Health Service Act. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 601.70 and including any updates to the status information since the annual report was prepared. Failure to comply with the REMS assessment provisions in section 505-1(g) could result in enforcement action.

We remind you that in addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of FDCA.

Prominently identify the submission containing the REMS assessments or proposed modifications with the following wording in bold, capital letters at the top of the first page of the submission:

BLA 125293
REMS ASSESSMENT

NEW SUPPLEMENT FOR BLA 125293
PROPOSED REMS MODIFICATION
REMS ASSESSMENT

NEW SUPPLEMENT (NEW INDICATION FOR USE) FOR BLA 125293
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

If you do not submit electronically, please send five copies of REMS-related submissions.

REPORTING REQUIREMENTS

You must submit adverse experience reports under the adverse experience reporting requirements for licensed biological products (21 CFR 600.80). You should submit postmarketing adverse experience reports to:

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Prominently identify all adverse experience reports as described in 21 CFR 600.80.

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

You must submit distribution reports under the distribution reporting requirements for licensed biological products (21 CFR 600.81).

You must submit reports of biological product deviations under 21 CFR 600.14. You should promptly identify and investigate all manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding, and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA-3486 to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
5901-B Ammendale Road
Beltsville, MD 20705-1266

Biological product deviations, sent by courier or overnight mail, should be addressed to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
10903 New Hampshire Avenue, Bldg. 51, Room 4206
Silver Spring, MD 20992-0002

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

All promotional claims must be consistent with and not contrary to approved labeling. You should not make a comparative promotional claim or claim of superiority over other products unless you have substantial evidence to support that claim.

LETTERS TO HEALTH CARE PROFESSIONALS

If you decide to issue a letter communicating important safety-related information about this drug product (e.g., a "Dear Health Care Professional" letter), we request that you submit, at least 24 hours prior to issuing the letter, an electronic copy of the letter to this BLA, to CDERMedWatchSafetyAlerts@fda.hhs.gov, and to the following address:

MedWatch Program
Office of Special Health Issues
Food and Drug Administration
10903 New Hampshire Ave
Building 32, Mail Stop 5353
Silver Spring, MD 20993

POST-ACTION FEEDBACK MEETING

New molecular entities and new biologics qualify for a post-action feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, call Ramani Sista, Regulatory Project Manager, at (301) 796-1236.

Sincerely,

/Curtis J. Rosebraugh, M.D., M.P.H./
Curtis J. Rosebraugh, M.D., M.P.H.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosures:
Package Insert with Medication Guide
REMS documents
Carton and Container Labels

EXHIBIT 5

US006783965B1

(12) **United States Patent**
Sherman et al.

(10) **Patent No.: US 6,783,965 B1**
(45) **Date of Patent: *Aug. 31, 2004**

(54) **AGGREGATE-FREE URATE OXIDASE FOR PREPARATION OF NON-IMMUNOGENIC POLYMER CONJUGATES**

(75) Inventors: **Merry R. Sherman**, San Carlos, CA (US); **Mark G. P. Saifer**, San Carlos, CA (US); **L. David Williams**, Fremont, CA (US)

(73) Assignee: **Mountain View Pharmaceuticals, Inc.**, Menlo Park, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **09/501,730**

(22) Filed: **Feb. 10, 2000**

(51) **Int. Cl.**[7] **C12N 9/04**; C12N 15/00; A61K 38/44; C07K 1/00; C07H 21/04

(52) **U.S. Cl.** **435/190**; 435/191; 435/440; 424/94.4; 536/23.2; 530/350

(58) **Field of Search** 435/190, 191, 435/440, 170; 424/94.4, 94.6; 536/23.2; 530/350, 413

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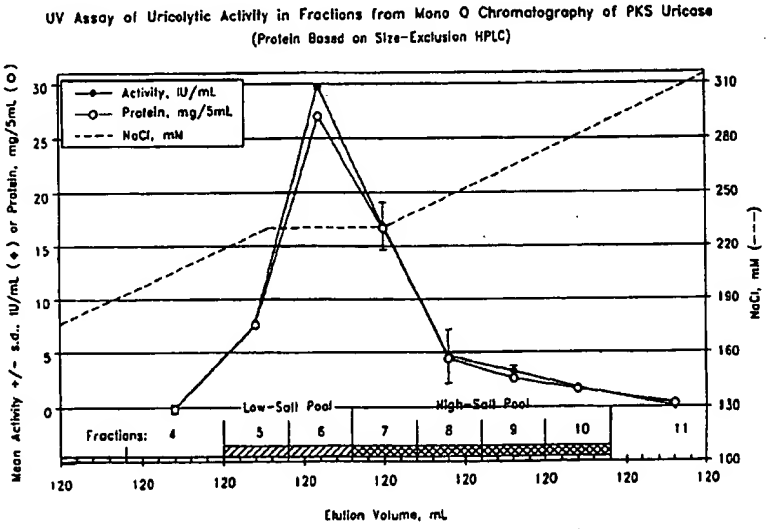
Primary Examiner—Ponnathapu Achutamurthy
Assistant Examiner—Yong Pak
(74) *Attorney, Agent, or Firm*—Sterne, Kessler, Goldstein & Fox P.L.L.C.

(57) **ABSTRACT**

A naturally occurring or recombinant protein, especially a mutein of porcine urate oxidase (uricase), that is essentially free of large aggregates can be rendered substantially non-immunogenic by conjugation with a sufficiently small number of strands of polymer such that the bioactivity of the protein is essentially retained in the conjugate. Such conjugates are unusually well suited for treatment of chronic conditions because they are less likely to induce the formation of antibodies and/or accelerated clearance than are similar conjugates prepared from protein preparations containing traces of large aggregates.

30 Claims, 6 Drawing Sheets



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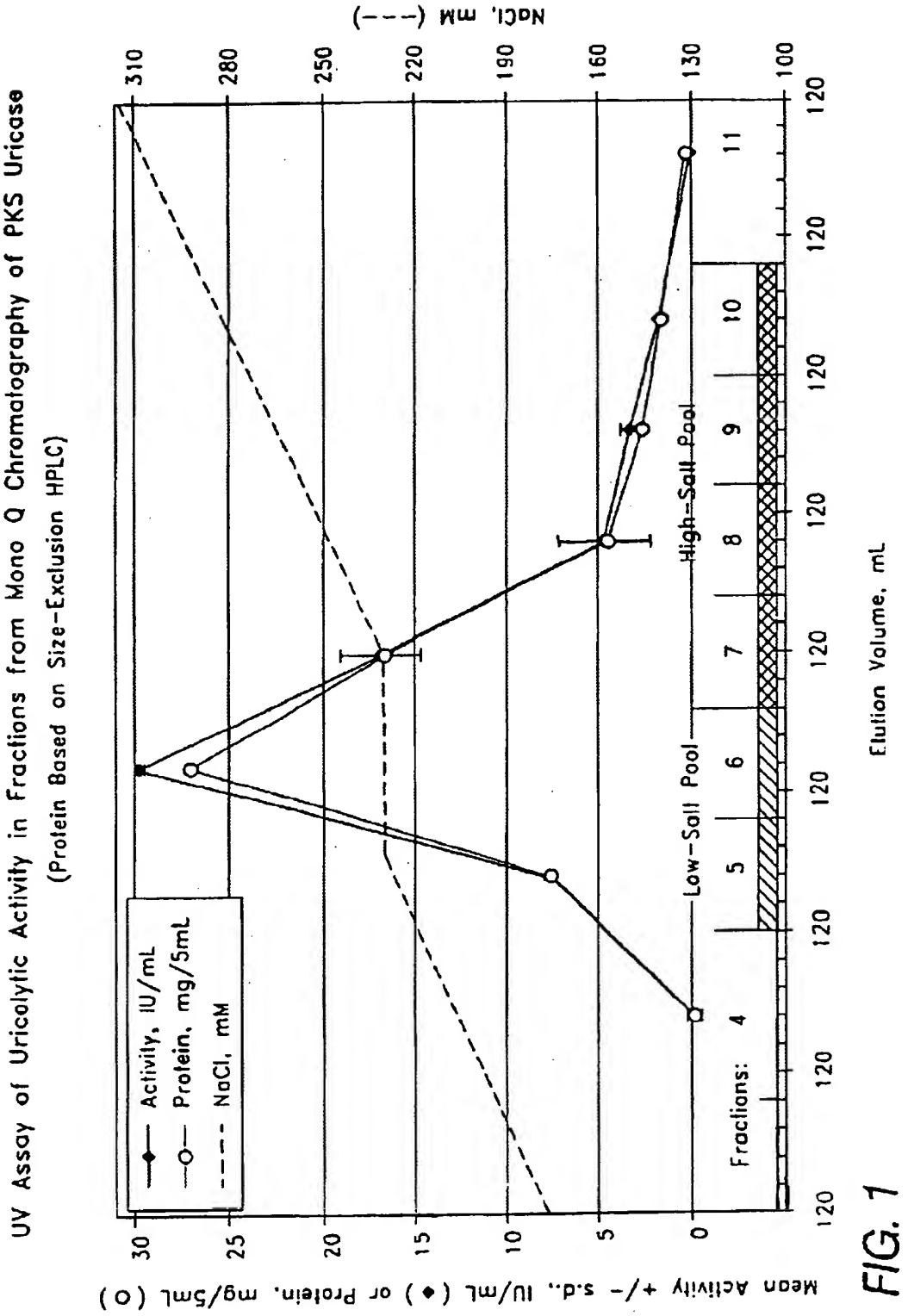
UV Assay of Uricolytic Activity in Fractions from Mono Q Chromatography of PKS Uricase
(Protein Based on Size-Exclusion HPLC)
Activity, IU/mL
Protein, mg/5mL
NaCl, mM
Mean Activity +/- s.d., IU/mL (◆) or Protein, mg/5mL (○)
NaCl, mM (---)
Fractions: 4 5 6 7 8 9 10 11
Low-Salt Pool
High-Salt Pool
Elution Volume, mL

FIG. 1

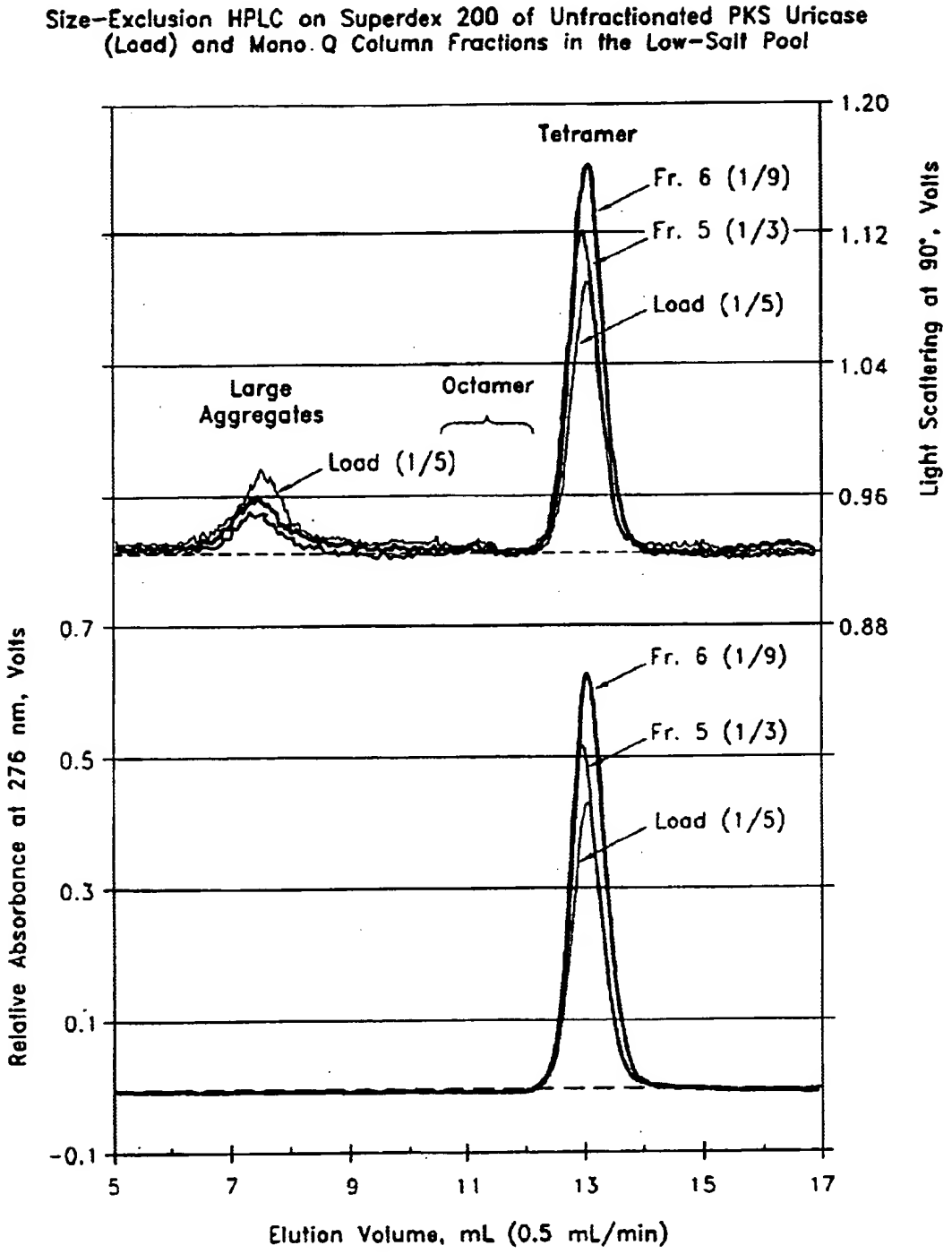
Size-Exclusion HPLC on Superdex 200 of Unfractionated PKS Uricase (Load) and Mono Q Column Fractions in the Low-Salt Pool
Tetramer
Fr. 6 (1/9)
Fr. 5 (1/3)
Load (1/5)
Large Aggregates
Octamer
Load (1/5)
Fr. 6 (1/9)
Fr. 5 (1/3)
Load (1/5)
1.20
1.12
1.04
0.96
0.88
0.7
0.5
0.3
0.1
-0.1
5
7
9
11
13
15
17
Relative Absorbance at 276 nm, Volts
Light Scattering at 90°, Volts
Elution Volume, mL (0.5 mL/min)

FIG. 2

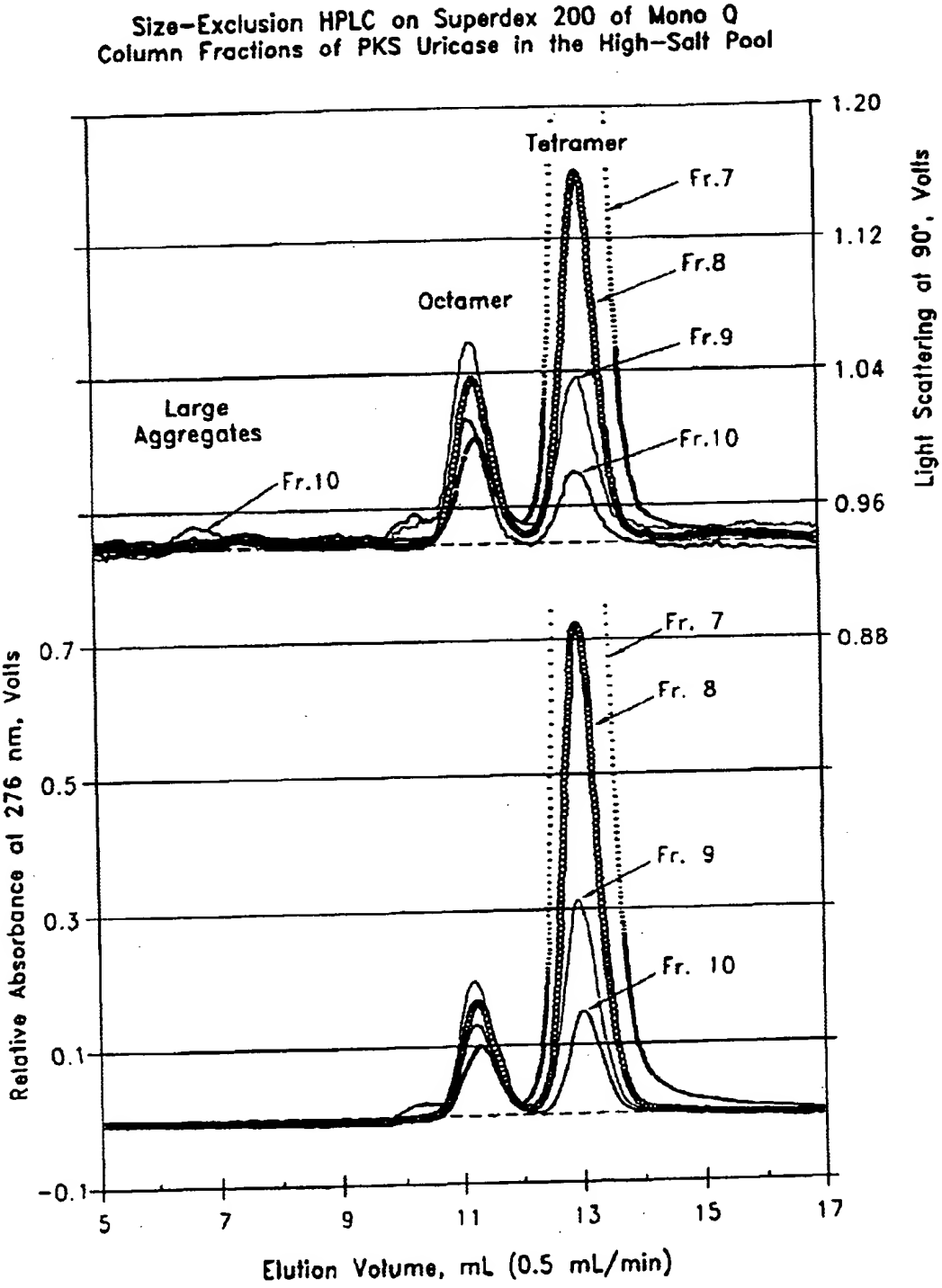
Size-Exclusion HPLC on Superdex 200 of Mono Q
Column Fractions of PKS Uricase in the High-Salt Pool
Tetramer
Octamer
Large
Aggregates
Fr.7
Fr.8
Fr.9
Fr.10
Fr.10
Fr. 7
Fr. 8
Fr. 9
Fr. 10
1.20
1.12
1.04
0.96
0.88
Light Scattering at 90°, Volts
0.7
0.5
0.3
0.1
-0.1
Relative Absorbance at 276 nm, Volts
5
7
9
11
13
15
17
Elution Volume, mL (0.5 mL/min)

FIG. 3

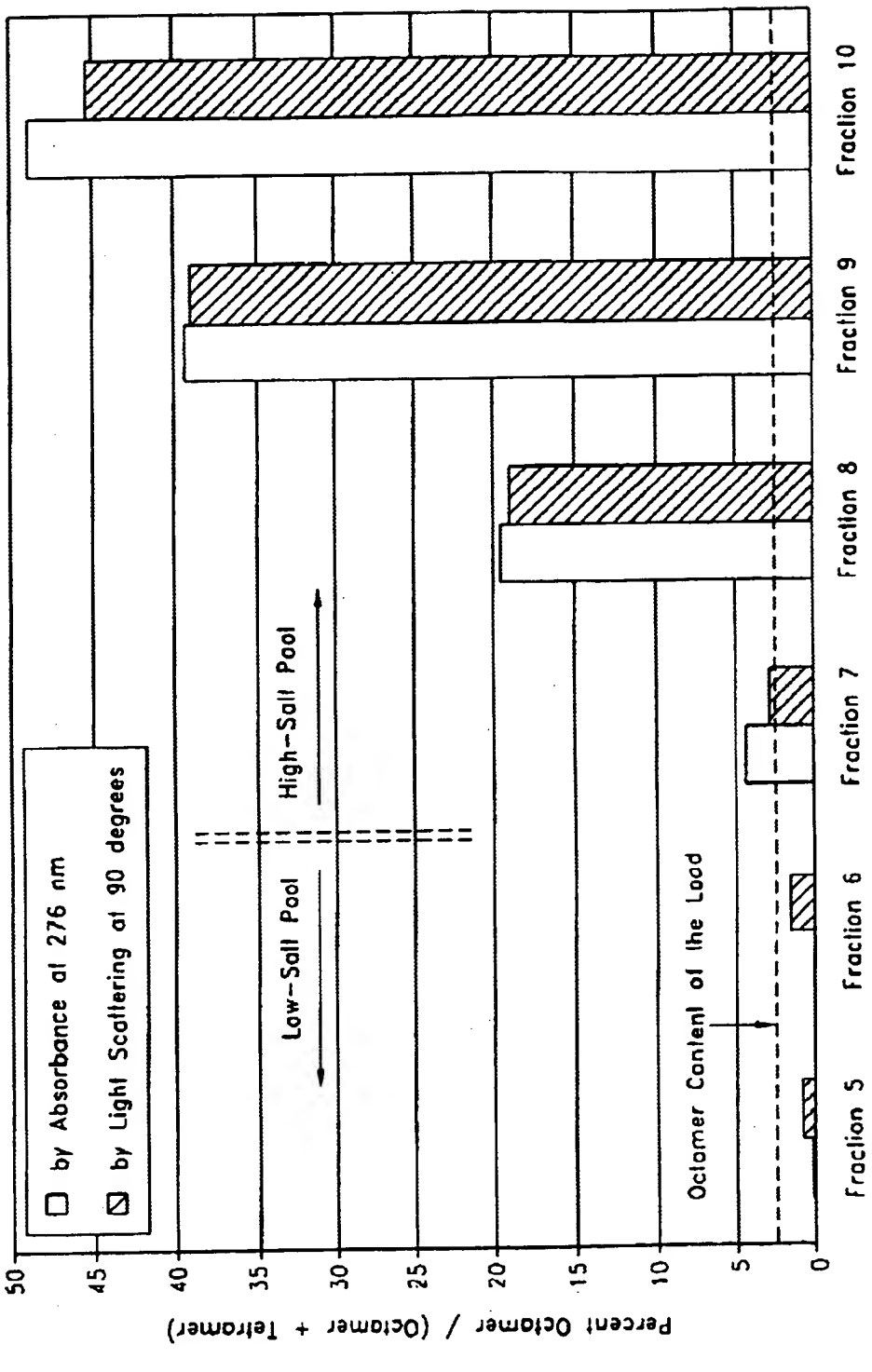
Octamer Content of Mono Q Column Fractions of PKS Uricase
by Absorbance at 276 nm
by Light Scattering at 90 degrees
High-Salt Pool
Low-Salt Pool
Octamer Content of the Load
Fraction 5
Fraction 6
Fraction 7
Fraction 8
Fraction 9
Fraction 10
Percent Octamer / (Octamer + Tetramer)
0
5
10
15
20
25
30
35
40
45
50

FIG. 4

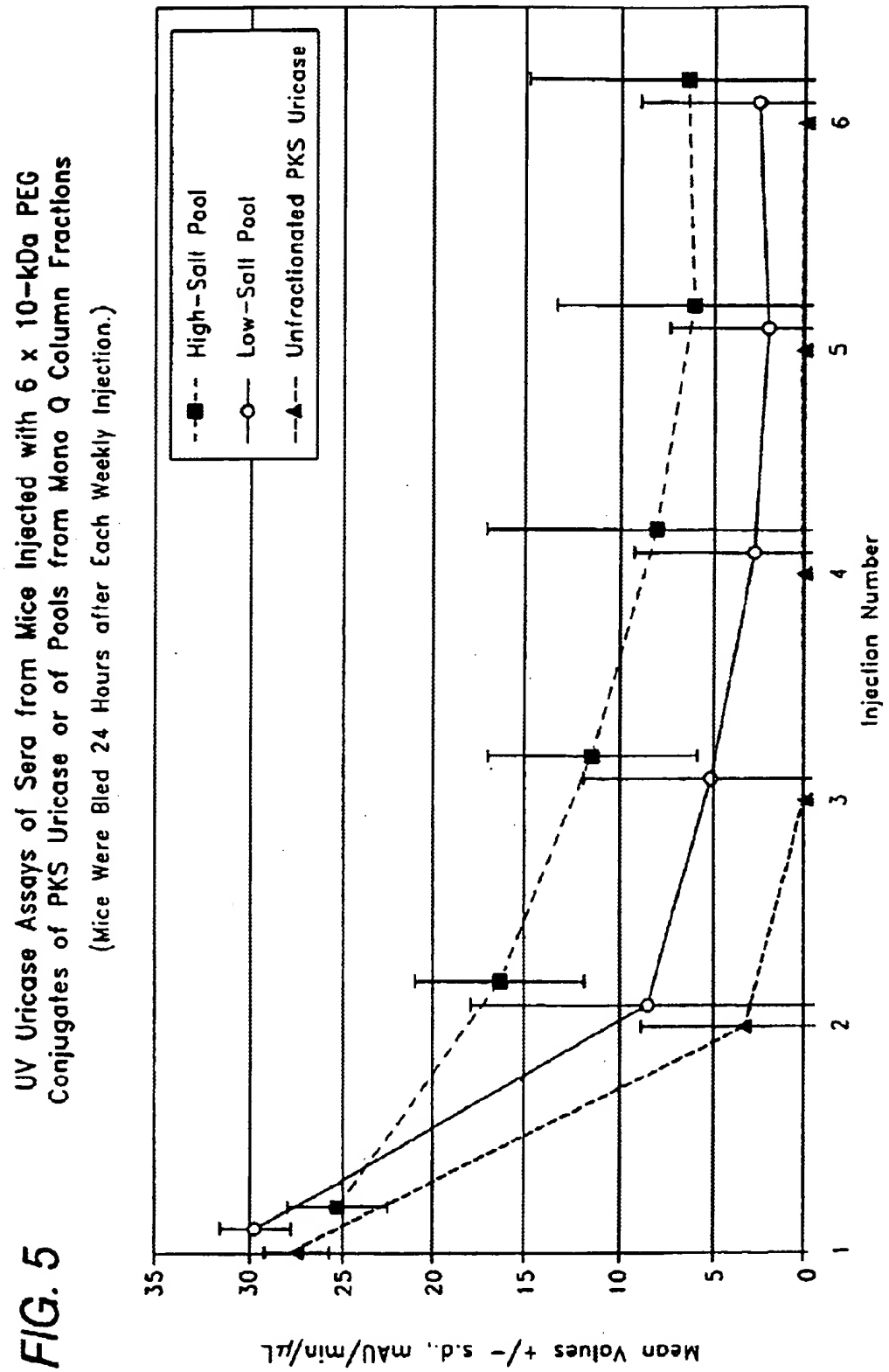
UV Uricase Assays of Sera from Mice Injected with 6 x 10-kDa PEG Conjugates of PKS Uricase or of Pools from Mono Q Column Fractions
(Mice Were Bled 24 Hours after Each Weekly Injection.)
High-Salt Pool
Low-Salt Pool
Unfractionated PKS Uricase
Mean Values +/- s.d., mAU/min/μL
Injection Number
0
5
10
15
20
25
30
35
1
2
3
4
5
6

FIG. 5

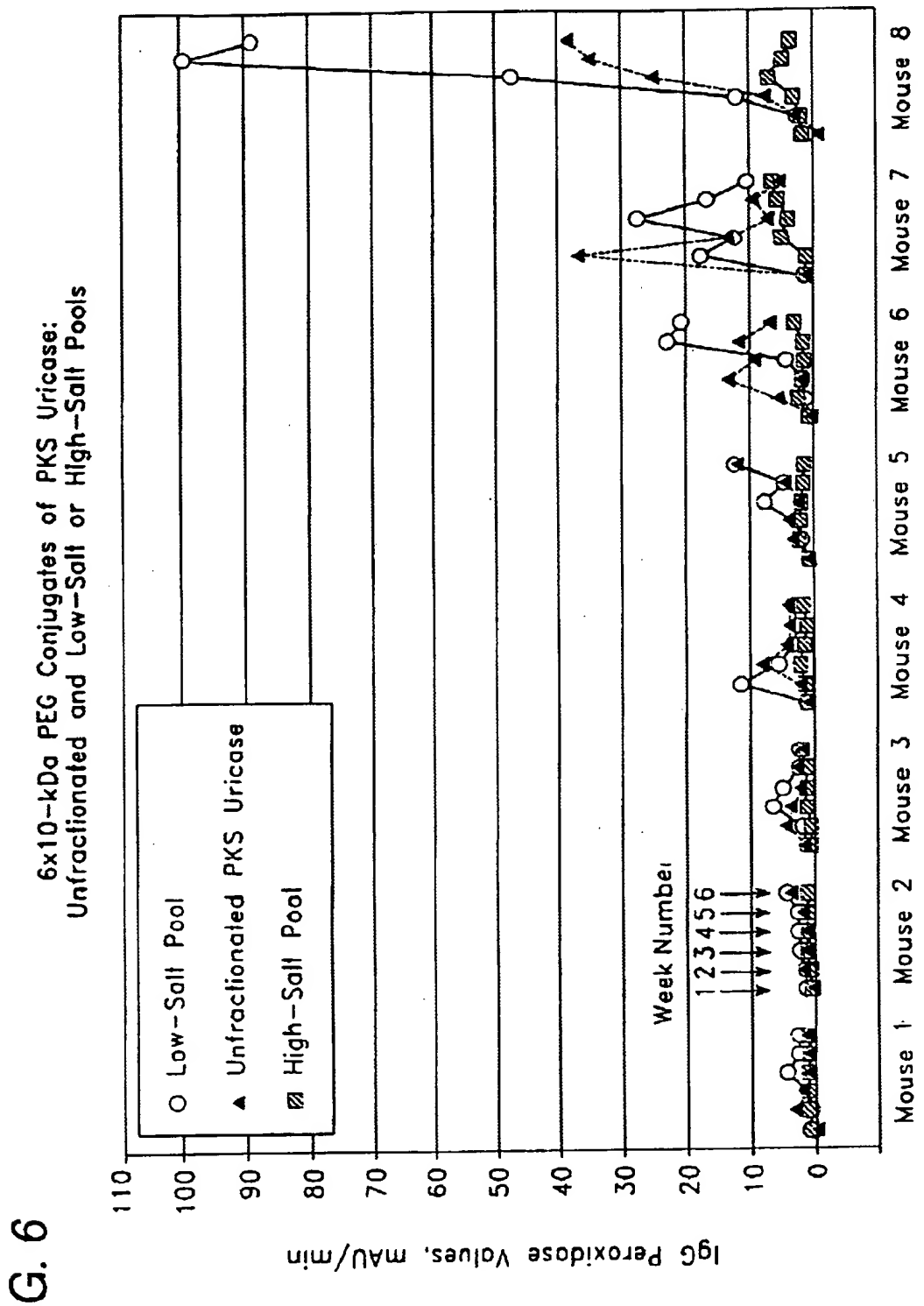
6x10-kDa PEG Conjugates of PKS Uricase:
Unfractionated and Low-Salt or High-Salt Pools
○ Low-Salt Pool
▲ Unfractionated PKS Uricase
▨ High-Salt Pool
log Peroxidose Values, mAU/min
110
100
90
80
70
60
50
40
30
20
10
0
Week Number
1 2 3 4 5 6
Mouse 1
Mouse 2
Mouse 3
Mouse 4
Mouse 5
Mouse 6
Mouse 7
Mouse 8

FIG. 6

AGGREGATE-FREE URATE OXIDASE FOR PREPARATION OF NON-IMMUNOGENIC POLYMER CONJUGATES

STATEMENT OF GOVERNMENT RIGHTS IN THE INVENTION

A portion of the research described in this application was made with support from the U.S.-Israel Binational Industrial Research and Development Foundation. Accordingly, the U.S. Government may have certain rights in the invention.

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to purification and chemical modification of proteins to prolong their circulating lifetimes and reduce their immunogenicity. More specifically, the invention relates to the removal of aggregates larger than octamers from urate oxidases (uricases) prior to conjugation of poly(ethylene glycols) or poly(ethylene oxides). This substantially eliminates uricase immunogenicity without compromising its uricolytic activity.

2. Description of the Related Art

Statements contained in this background section do not constitute an admission of prior art, but instead reflect the inventors' own subjective comments on and interpretations of the state of the art at the time the invention was made. These interpretations may include personal, heretofore undisclosed, insights of the inventors, which insights were not themselves part of the prior art.

Urate oxidases (uricases; E.C. 1.7.3.3) are enzymes that catalyze the oxidation of uric acid to a more soluble product, allantoin, a purine metabolite that is more readily excreted. Humans do not produce enzymatically active uricase, as a result of several mutations in the gene for uricase acquired during the evolution of higher primates. Wu, X, et al., (1992) *J Mol Evol* 34:78–84. As a consequence, in susceptible individuals, excessive concentrations of uric acid in the blood (hyperuricemia) and in the urine (hyperuricosuria) can lead to painful arthritis (gout), disfiguring urate deposits (tophi) and renal failure. In some affected individuals, available drugs such as allopurinol (an inhibitor of uric acid synthesis) produce treatment-limiting adverse effects or do not relieve these conditions adequately. Hande, K R, et al., (1984) *Am J Med* 76:4–56; Fam, A G, (1990) *Baillière's Clin Rheumatol* 4:177–192. Injections of uricase can decrease hyperuricemia and hyperuricosuria, at least transiently. Since uricase is a foreign protein in humans, however, even the first injection of the unmodified protein from *Aspergillus flavus* has induced anaphylactic reactions in several percent of treated patients (Pui, C-H, et al., (1997) *Leukemia* 11:1813–1816), and immunologic responses limit its utility for chronic or intermittent treatment. Donadio, D, et al., (1981) *Nouv Presse Méd* 10:711–712; Leaustic, M, et al., (1983) *Rev Rhum Mal Osteoartic* 50:553–554.

U.S. patent application Ser. No. 09/370,084 and published International Application No. PCT/US99/17514, the entire contents of which are incorporated herein by reference, disclose poly (ethylene glycol)-urate oxidase (PEG-uricase) that retains at least about 75% of the uricolytic activity of unconjugated uricase and has substantially reduced immunogenicity. In one such purified uricase, each subunit is covalently linked to an average of 2 to 10 strands of PEG, wherein each molecule of PEG may have a molecular weight between about 5 kDa and 100 kDa.

The aggregation of proteins is known to increase their immunogenicity. This understanding has contributed to the development of methods for intentionally aggregating proteins by treatments such as thermal denaturation and cross-linking by exposure to glutaraldehyde prior to use in the preparation of vaccines or for immunization of animals to produce antisera.

Unintentional aggregation of proteins has also been recognized as contributing to immunization or sensitization during clinical use of therapeutic proteins, e.g. for human gamma globulin (Henney et al. (1968) *N. Engl. J Med.* 278:2244–2246) and for human growth hormone (Moore et al. (1980) *J Clin. Endocrinol. Metab.* 51:691–697). The contribution of aggregates to the immunogenicity of human interferon alpha has been demonstrated in BALB/c mice (Braun et al. (1997) *Pharm. Res.* 14:1472–1478) and an enzyme-linked immunosorbent assay (ELISA) has been developed for their measurement (Braun et al. (1997) *Pharm. Res.* 14:1394–1400).

In contrast to the known effects of aggregation on the immunogenicity of proteins, there are not reports of the effect of aggregation on the immunogenicity of proteins conjugated to poly(alkylene glycols) such as PEG. There is a need for poly(alkylene glycol)-uricase conjugates that substantially eliminates uricase immunogenicity without compromising its uricolytic activity. The present invention provide such compositions.

SUMMARY OF THE INVENTION

Conjugation of proteins with poly(alkylene glycols), especially PEG, produces conjugates with reduced immunogenicity and increased persistence in the bloodstream. In attempting to produce substantially non-immunogenic conjugates of uricase that retain substantially all of the uricolytic activity of the unmodified uricase preparation, it was discovered that traces of large aggregates of uricase in the starting material were surprisingly effective at provoking both antibody formation and accelerated clearance from the circulation, both of which are deleterious, after repeated injections of PEG conjugates prepared from uricase containing such aggregates. Surprisingly, the present inventors found that the increased immunogenicity and accelerated clearance were not due to the presence of well-defined, moderate-sized aggregates of the uricase subunit that are larger than the native tetramer, e.g. aggregates containing eight subunits (octamers). The octameric form of uricase is present at sufficiently high concentrations in most preparations of uricase to be detectable by its absorbance of UV light, e.g. at 214 nm or 276 nm, or by its contribution to the refractive index or other measurements of protein concentration. Nevertheless, the octamers themselves were found to contribute minimally to the immunogenicity and accelerated clearance of PEG-uricase conjugates, in contrast with the much smaller quantities of the much larger aggregates that are undetectable by UV absorbance under the conditions tested but are readily detected by static (Raleigh) or dynamic light scattering. Therefore, the removal of such traces of very large aggregates prior to conjugation with PEG was found to decrease the immunogenicity and the accelerated clearance of the resultant PEG-uricase conjugates to a surprising extent.

One embodiment of the present invention is purified urate oxidase (uricase) substantially free of aggregates larger than octamers. Preferably, the uricase is mammalian uricase. More preferably, the uricase is porcine liver, bovine liver or ovine liver uricase. In one aspect of this preferred embodiment, the uricase is recombinant. In another aspect of this preferred embodiment, the uricase has substantially the

sequence of porcine, bovine, ovine or baboon liver uricase. Advantageously, the uricase is chimeric. Preferably, the uricase is PKS uricase. In another aspect of this preferred embodiment, the uricase has substantially the sequence of baboon liver uricase in which tyrosine 97 has been replace by histidine. Preferably, the uricase comprises an amino terminus and a carboxy terminus, and wherein the uricase is truncated at one terminus or both termini. Advantageously, the uricase is a fungal or microbial uricase. Preferably, the fungal or microbial uricase is isolated from *Aspergillus flavus, Arthrobacter globiformis*, Bacillus sp. or *Candida utilis*, or is a recombinant enzyme having substantially the sequence of one of said uricases. Alternatively, the uricase is an invertebrate uricase. Preferably, the invertebrate uricase is isolated from *Drosophila melanoguster* or *Drosophila pseudoobscura*, or is a recombinant enzyme having substantially the sequence of one of said uricases. In another aspect of this preferred embodiment, the uricase is a plant uricase. Preferably, the plant uricase is isolated from root nodules of *Glycine max* or is a recombinant enzyme having substantially the sequence of the uricase.

In one aspect of this preferred embodiment, the uricase described above is conjugated to poly(ethylene glycol) or poly(ethylene oxide), under conditions such that the uricase in the conjugate is substantially free of aggregates larger than octamers. Preferably, the uricase is conjugated to poly(ethylene glycol) or poly(ethylene oxide) via a urethane (carbamate), secondary amine or amide linkage. In one aspect of this preferred embodiment, the poly(ethylene glycol) is monomethoxy poly(ethylene glycol). In another aspect of this preferred embodiment, the poly(ethylene glycol) or poly(ethylene oxide) has a molecular weight between about 5 kDa and 30 kDa. Preferably, the poly (ethylene glycol) or poly(ethylene oxide) has a molecular weight between about 10 kDa and 20 kDa. Advantageously, the average number of strands of said poly(ethylene glycol) or poly(ethylene oxide) is between about 2 and 12 per uricase subunit. More advantageously, the average number of strands of said poly(ethylene glycol) or poly(ethylene oxide) is between about 6 and 10 per uricase subunit. Most advantageously, the average number of strands of said poly(ethylene glycol) or poly(ethylene oxide) is between about 7 and 9 per uricase subunit. Preferably, the poly (ethylene glycol) or poly(ethylene oxide) is linear. Alternatively, the poly(ethylene glycol) or poly(ethylene oxide) is branched.

The present invention also provides a pharmaceutical composition for lowering uric acid levels in a body fluid or tissue, comprising the uricase conjugate described above and a pharmaceutically acceptable carrier. Preferably, the composition is stabilized by lyophilization and dissolves upon reconstitution to provide solutions suitable for parenteral administration.

Another embodiment of the invention is a method for purifying uricase having reduced immunogenicity, comprising the step of separating uricase aggregates larger than octamers in uricase fractions, and excluding such aggregates from the purified uricase. Preferably, the separating step comprises the step of detecting aggregates larger than octamers from at least a portion of the uricase fractions and excluding the fractions containing the aggregates. Advantageously, the detecting step comprises measurement of light scattering.

The present invention also provides isolated uricase prepared by the method described above.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** illustrates uricase activity, total protein and salt concentrations in fractions from a Pharmacia Biotech Mono Q (1×10 cm) anion exchange column. Uricase activity was measured at room temperature by monitoring the decrease in absorbance at 292 nm of 100 μM uric acid in 200 mM sodium borate, pH 9.2. Total protein was determined from the area under the curve of the absorbance peak of uricase in size-exclusion HPLC analyses. Salt concentrations were calculated from the conductivities at room temperature using a standard curve for NaCl in the same buffer.

FIG. **2** illustrates size-exclusion HPLC analysis on a Pharmacia Superdex 200 column (1×30 cm) of the load and selected fractions from a preparative Mono Q chromatography of porcine uricase containing the mutations R291K and T301S (PKS uricase) showing data obtained by a light-scattering detector at 90° C. (upper curves) and by absorbance at 276 nm (lower curves). The different signal strengths of the tetrameric, octameric and more highly aggregated forms of uricase in the unfractionated sample (load) and the various fractions are evident. The load was diluted ⅓ with Mono Q column buffer, fraction 5 was diluted ⅓ and fraction 6 was diluted ⅙. Fractions 5 and 6 were combined to form the "low salt pool."

FIG. **3** illustrates size-exclusion analyses of fractions from the Mono Q column in FIG. **1**, showing data obtained by a light-scattering detector at 90° and by absorbance at 276 nm, as in FIG. **2**. The fractions shown in this figure were used to form the "high salt pool", from which PEG conjugates were prepared and injected into BALB/c mice. The resultant serum activities and immunologic responses in BALB/c mice are shown in FIGS. **5** and **6**.

FIG. **4** illustrates octamer content, determined by absorbance at 276 nm and by light scattering at 90°, calculated from the data in FIGS. **2** and **3**, of unfractionated PKS uricase and of selected fractions from the preparative MonoQ column chromatography of PKS uricase (FIG. **1**).

FIG. **5** illustrates UV assays, as in FIG. **1**, of uricase activity after a 4-hour incubation at 37° C., in sera drawn 24 hours after each of six weekly injections of 6×10-kDa PEG conjugates of PKS uricase or of pools from Mono Q column fractions.

FIG. **6** illustrates ELISA analyses of IgG antibody formation against PEG conjugates of PKS uricase and against PEG conjugates of the pools of fractions from the Mono Q column shown in FIG. **1**, in sera drawn 24 hours after each of six weekly injections of female BALB/c mice with 0.2 mg of uricase protein per 20 grams of body weight. For each mouse, data from bleedings 24 hours after the first through sixth injections are shown from left to right. The assay conditions are described in Example 6. Data for the eight mice in each group were arranged in order of increasing immune response, from left to right.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

Previous studies have shown that when a significant reduction in the immunogenicity and/or antigenicity of uricase is achieved by conjugation with PEG (PEGylation), it is invariably associated with a substantial loss of uricolytic activity. The present invention includes the observation that traces of aggregates of urate oxidases larger than octamers substantially contribute to immunogenicity and the induction of accelerated clearance of PEG-uricase conjugates. This discovery is most likely applicable to proteins other than uricases, including interferons and growth factors.

The safety, convenience and cost-effectiveness of biopharmaceuticals are all adversely impacted by decreases in their potencies and the resultant need to increase the admin-

istered dose. Thus, there is a need for a safe and effective alternative means for lowering elevated levels of uric acid in body fluids, including blood and urine. The present invention provides a method for producing uricase that excludes uricase aggregates larger than octamers for use in the synthesis of PEG-uricase. This PEG-uricase retains all or nearly all of the uricolytic activity of the unmodified enzyme. The present invention also provides purified uricase substantially free of aggregates larger than octamers. The term "substantially free" indicates that the purified uricase comprises no more than about 2%, and preferably no more than about 1% of aggregates larger than octamers.

The present invention provides a method for purifying uricase such that aggregates larger then octamers are excluded from the purified preparation. Because these larger aggregates are highly immunogenic, their presence in the purified uricase preparation is undesirable. The method involves monitoring column fractions by light scattering rather than or in addition to ultraviolet absorbance at 280 nm, because the aggregates may be too dilute to be detected by ultraviolet absorbance. The purified uricase is then conjugated to water-soluble polymers, preferably poly(ethylene glycols) or poly(ethylene oxides) as described in copending U.S. application Ser. No. 09/370,084, the entire contents of which are incorporated herein by reference.

The removal of aggregated uricase from a preparation consisting predominantly of tetrameric uricase can be accomplished by any of the methods know to those skilled in the art, including size-exclusion chromatography, ion-exchange chromatography, ultrafiltration through a microporous membrane and centrifugation, including ultra-centrifugation. The separation method may include separation and analysis of fractions and the rejection or exclusion of those fractions containing excessive quantities of large aggregates. The resultant uricase preparation is better suited for the synthesis of substantially non-immunogenic conjugates of uricase than is the unfractionated uricase. For chronic administration, it is important that PEG conjugates of proteins, e.g. PEG-uricase, have low immunogenicity and do not provoke progressively more rapid clearance from the bloodstream after repeated doses.

The invention also provides pharmaceutical compositions of the polymer-uricase conjugates. These conjugates are substantially non-immunogenic and retain at least 75%, preferably 85%, and more preferably 95% or more of the uricolytic activity of the unmodified enzyme. Uricases suitable for conjugation to water-soluble polymers include naturally occurring urate oxidases isolated from bacteria, fungi and the tissues of plants and animals, both vertebrates and invertebrates, as well as recombinant forms of uricase, including mutated, hybrid, and/or truncated enzymatically active variants of uricase. Water-soluble polymers suitable for use in the present invention include linear and branched poly(ethylene glycols) or poly(ethylene oxides), all commonly known as PEGs. Examples of branched PEG are the subject of U.S. Pat. No. 5,643,575. One preferred example of linear PEG is monomethoxyPEG, of the general structure $CH_3O—(CH_2CH_2O)_nH$, where n varies from about 100 to about 2,300

One embodiment of the present invention is a conjugate of urate oxidase (uricase) that retains at least about 75% of the uricolytic activity of unconjugated uricase and has substantially reduced immunogenicity. The uricase of this aspect of the invention may be recombinant. Whether recombinant or not, the uricase may be of mammalian origin. In one aspect of this embodiment, the uricase may be porcine, bovine or ovine liver uricase. In another aspect of this embodiment, the uricase may be chimeric. The chimeric uricase may contain portions of porcine liver and/or baboon liver uricase. For example, the chimeric uricase may be porcine uricase containing the mutations R291K and T301S (PKS uricase). Alternatively, the uricase may be baboon liver uricase in which tyrosine 97 has been replaced by histidine, whereby the specific activity of the uricase may be increased by at least about 60%. The uricase of the invention, whatever the origin, may also be in a form that is truncated, either at the amino terminal, or at the carboxyl terminal, or at both terminals. Likewise, the uricase may be fungal or microbial uricase. In one aspect of this embodiment, the fungal or microbial uricase may be a naturally occurring or recombinant form of uricase from *Aspergillus flavus, Arthrobacter globiformis*, Bacillus sp. or *Candida utilis*. Alternatively, the uricase may be an invertebrate uricase, such as, for example, a naturally occurring or recombinant form of uricase from *Drosophila melanogaster* or *Drosophila pseudoobscura*. The uricase of the invention may also be a plant uricase, for example, a naturally occurring or recombinant form of uricase from soybean root nodule (*Glycine max*). The PEG may have an average molecular weight between about 5 kDa and 100 kDa; preferably the PEG may have an average molecular weight between about 8 kDa and 60 kDa; more preferably, the PEG may have an average molecular weight between about 10 kDa and about 40 kDa, such as, for example, 10 to 20 kDa. The average number of covalently coupled strands of PEG may be 2 to 12 strands per uricase subunit; preferably, the average number of covalently coupled strands may be 6 to 10 per subunit; more preferably, the average number of strands of PEG may be 7 to 9 per subunit. In one aspect of this embodiment, the uricase may be tetrameric. The strands of PEG may be covalently linked to uricase via urethane (carbamate) linkages, secondary amine linkages, and/or amide linkages. When the uricase is a recombinant form of any of the uricases mentioned herein, the recombinant form may have substantially the sequence of the naturally occurring form.

One preferred mammalian uricase is recombinant pig-baboon chimeric uricase, composed of portions of the sequences of pig liver and baboon liver uricase, both of which were first determined by Wu, et al., (1989). One example of such a chimeric uricase contains the first 288 amino acids from the porcine sequence (SEQ ID NO: 1) and the last 16 amino acids from the baboon sequence (SEQ ID NO: 2). Since the latter sequence differs from the porcine sequence at only two positions, having a lysine (K) in place of arginine at residue 291 and a serine (S) in place of threonine at residue 301, this mutant is referred to as pig-K-S or PKS uricase (SEQ ID NO: 3). PKS uricase has one more lysine residue and, hence, one more potential site of PEGylation than either the porcine or baboon sequence.

The cDNAs for various mammalian uricases, including PKS uricase, were subcloned and the optimal conditions were determined for expression in *E. coli*, using standard methods. See Erlich, H A, (Ed.) (1989) *PCR Technology. Principles and Applications for DNA Amplification.* New York: Stockton Press; Sambrook, J, et al., (1989) *Molecular Cloning. A Laboratory Manual, Second Edition.* Cold Spring Harbor, NY: Cold Spring Harbor Laboratory Press. The recombinant uricases were extracted, purified and their stability and activity were assessed using a modification of standard assays. See Fridovich, I, (1965) *J Biol Chem* 240:2491–2494; Nishimura, et al., (1979), and Examples 1 and 5.

In one embodiment of the invention, uricase may be conjugated via a biologically stable, nontoxic, covalent

linkage to a relatively small number of strands of PEG. Such linkages may include urethane (carbamate) linkages, secondary amine linkages, and amide linkages. Various activated PEGs suitable for such conjugation are available commercially from Shearwater Polymers, Huntsville, AL.

For example, urethane linkages to uricase may be formed by incubating uricase in the presence of the succinimidyl carbonate (SC) or p-nitrophenyl carbonate (NPC) derivative of PEG. SC-PEG may be synthesized using the procedure described in U.S. Pat. No. 5,612,460, which is hereby incorporated by reference. NPC-PEG may be synthesized by reacting PEG with p-nitrophenyl chloroformate according to methods described in Veronese, FM, et al., (1985) *Appl Biochem Biotechnol* 11:141–152, and in U.S. Pat. No. 5,286,637, which is hereby incorporated by reference. The methods described in the '637 patent are adapted to PEGs of higher molecular weight by adjusting the concentrations of the reactants to maintain similar stoichiometry. An alternative method of synthesis of NPC-PEG is described by B üttner, W, et al., East German Patent Specification DD 279 486 A1.

Amide linkages to uricase may be obtained using an N-hydroxysuccinimide ester of a carboxylic acid derivative of PEG (Shearwater Polymers). Secondary amine linkages may be formed using 2,2,2-trifluoroethanesulfonyl PEG (tresyl PEG; Shearwater Polymers) or by reductive alkylation using PEG aldehyde (Shearvater Polymers) and sodium cyanoborohydride.

In conjugates containing PEG with a molecular weight of 10 kDa, the maximum number of strands of PEG that were coupled per subunit, while retaining at least 75% of the uricolytic activity of the unmodified enzyme, was about 12 strands for mammalian uricases (e.g. PKS uricase, a mutein of porcine uricase; see assay conditions in Example 5). The latter extent of PEGylation corresponds to about 40% of the total amino groups. In one embodiment of the invention, the average number of strands of PEG coupled per uricase subunit is between about 2 and 12. In a preferred embodiment, the average number of strands of PEG coupled per uricase subunit is between about 6 and 10. In a more preferred embodiment, the average number of covalently linked strands of PEG per uricase subunit is between about 7 and 9. In another embodiment, the molecular weight of PEG used for the coupling reaction is between about 5 kDa and 30 kDa, preferably between about 10 kDa and 20 kDa.

There are several factors that may affect the choice of the optimal molecular weight and number of strands of PEG for coupling to a given form of uricase. In general, the reduction or elimination of immunogenicity without substantial loss of uricolytic activity may require the coupling of relatively more strands of PEG of lower molecular weight, compared to relatively fewer strands of PEG of higher molecular weight. Likewise, each different form of uricase may have a different optimum with respect to both the size and number of strands. The optimal number of strands of PEG and PEG molecular weight can be readily determined using the methods described herein.

When PEG conjugates of mammalian uricase were prepared from the purified tetrameric and octameric forms of the enzyme (containing four or eight subunits of approximately 35 kDa), they displayed profoundly reduced immunogenicity in mice, in contrast to the moderate immunogenicity of PEG conjugates of uricase preparations containing large aggregates (see FIG. 6) and the very high immunogenicity of the unmodified enzyme.

Purified preparations of naturally occurring and recombinant uricases usually contain a mixture of very large aggregates of the enzyme, in addition to the tetrameric (140-kDa) and the octameric (280-kDa) forms. The percentage of each uricase preparation that is in either the tetrameric or octameric form generally varies from about 20% to 95% (see FIGS. **2–4**). Despite evidence that unPEGylated aggregates of several other proteins are highly immunogenic (see, e.g., Moore, W V, et al., (1980) *J Clin Endocrinol Metab* 51:691–697), previous studies of PEG-uricase do not describe any efforts to limit the content of aggregates, suggesting that the potential immunogenicity of the PEG-modified aggregates was not considered. On the basis of the observations of the present inventors, it appears likely that such aggregates were present in the enzyme preparations used for previous syntheses of PEG-uricase. Their presence may have rendered the task of preparing non-immunogenic conjugates more difficult. It also appears that the large losses of uricolytic activity observed in previous efforts to PEGylate uricase were related to the large number of strands of low molecular weight PEG that were coupled. On the other hand, the methods of uricase purification and PEGylation described herein permit the covalent attachment of as many as 12 strands of PEG per subunit while retaining more than 75% of the uricolytic activity, at least for certain uricases, e.g., PKS uricase (a mutein of porcine uricase) and the enzyme from thermophilic Bacillus sp.

In another preferred embodiment, substantially all large aggregates of the enzyme may be removed by ion-exchange chromatography (FIGS. **1–3**) or size-exclusion chromatography at a pH between about 9 and 10.5, preferably 10.2, prior to conjugation of the resulting substantially aggregate-free preparation of uricase to PEG. The molecular weight of the uricase in each fraction from the preparative column may be monitored by any size-dependent analytical technique, including, for example, HPLC, conventional size-exclusion chromatography, centrifugation, light scattering, capillary electrophoresis or gel electrophoresis in a non-denaturing buffer. For aggregate-free uricase isolated using size-exclusion chromatography, fractions containing only the 140-kDa and 280-kDa forms of the enzyme may be pooled and used for conjugation to PEG. For tetrameric plus octameric uricase isolated using ion-exchange chromatography, fractions from the ion-exchange column may be analyzed with respect to size to determine which fractions contain substantial amounts of the tetrameric and octameric forms without the large aggregates detected by light scattering. In the purified product, the undesirable large aggregates may thus constitute as little as about 1%, or less, of the total uricase.

The results presented herein indicate that, even when extensively PEGylated, forms of PKS uricase larger than the octamer provoke accelerated clearance (FIG. **5**) and are somewhat immunogenic in mice (FIG. **6**). In contrast, conjugates prepared from uricase that is essentially free of large aggregates (detectable by light scattering) could be reinjected at least six times at one-week intervals with much less evidence of accelerated clearance rates (FIG. **5**) and without the detectable formation of antibodies, as measured by a sensitive enzyme-linked immunoassay (FIG. **6**). The use of highly purified tetrameric or octameric uricase further distinguishes the improved conjugates of the present invention from the PEG-uricase preparations described previously. In contrast, the presence of a significant content of large aggregates in the uricase preparations used by some previous investigators may have led them to couple large numbers of strands of PEG in efforts to suppress the immunogenicity. Consequently, the enzymatic activity of the resultant conjugates was decreased substantially.

The PEG-uricase conjugates of the present invention are useful for lowering the levels of uric acid in the body fluids and tissues of mammals, preferably humans, and can thus be used for treatment of elevated uric acid levels associated with conditions including gout, tophi, renal insufficiency, organ transplantation and malignant disease. PEG-uricase conjugates may be injected into a mammal having excessive uric acid levels by any of a number of routes, including intravenous, subcutaneous, intradermal, intramuscular and intraperitoneal routes. Alternatively, they may be aerosolized and inhaled. See Patton, JS, (1996) *Adv Drug Delivery Rev* 19:3–36 and U.S. Pat. No. 5,458,135. The effective dose of PEG-uricase of the present invention will depend on the level of uric acid and the size of the individual. In one embodiment of this aspect of the invention, PEG-uricase is administered in a pharmaceutically acceptable excipient or diluent in an amount ranging from about 10 μg to about 1 g. In a preferred embodiment, the amount administered is between about 100 μg and 500 mg. More preferably, the conjugated uricase is administered in an amount between 1 mg and 100 mg, such as, for example, 5 mg, 20 mg or 50 mg. Masses given for dosage amounts of the embodiments refer to the amount of protein in the conjugate.

Pharmaceutical formulations containing PEG-uricase can be prepared by conventional techniques, e.g., as described in Gennaro, AR (Ed.) (1990) *Remington's Pharmaceutical Sciences*, 18th Edition, Easton, Pa.: Mack Publishing Co. Suitable excipients for the preparation of injectable solutions include, for example, phosphate buffered saline, lactated Ringer's solution, water, polyols and glycerol. Pharmaceutical compositions for parenteral injection comprise pharmaceutically acceptable sterile aqueous or non-aqueous liquids, dispersions, suspensions, or emulsions as well as sterile powders for reconstitution into sterile injectable solutions or dispersions just prior to use. These formulations may contain additional components, such as, for example, preservatives, solubilizers, stabilizers, wetting agents, emulsifiers, buffers, antioxidants and diluents.

PEG-uricase may also be provided as controlled-release compositions for implantation into an individual to continually control elevated uric acid levels in body fluids. For example, polylactic acid, polyglycolic acid, regenerated collagen, poly-L-lysine, sodium alginate, gellan gum, chitosan, agarose, multilamellar liposomes and many other conventional depot formulations comprise bioerodible or biodegradable materials that can be formulated with biologically active compositions. These materials, when implanted or injected, gradually break down and release the active material to the surrounding tissue. For example, one method of encapsulating PEG-uricase comprises the method disclosed in U.S. Pat. No. 5,653,974, which is hereby incorporated by reference. The use of bioerodible, biodegradable and other depot formulations is expressly contemplated in the present invention. The use of infusion pumps and matrix entrapment systems for delivery of PEG-uricase is also within the scope of the present invention. PEG-uricase may also advantageously be enclosed in micelles or liposomes. Liposome encapsulation technology is well known in the art. See, e.g., Lasic, D, et al., (Eds.) (1995) *Stealth Liposomes*. Boca Raton, Fla.: CRC Press.

The PEG-uricase pharmaceutical compositions of the invention will decrease the need for hemodialysis in patients at high risk of urate-induced renal failure, e.g., organ transplant recipients (see Venkataseshan, VS, et al., (1990) *Nephron* 56:317–321) and patients with some malignant diseases. In patients with large accumulations of crystalline urate (tophi), such pharmaceutical compositions will improve the quality of life more rapidly than currently available treatments.

The following examples, which are not to be construed as limiting the invention in any way, illustrate the various aspects disclosed above. These examples describe PEG-uricases prepared by coupling activated PEG (e.g., the p-nitrophenyl carbonate derivative) to a mutein of porcine uricases. These examples provide guidance to one of ordinary skill in the art for producing substantially non-immunogenic conjugates of uricase that retain at least about 75% of the uricolytic activity of the unmodified enzyme and are well suited for chronic administration.

EXAMPLE 1

Preparative Ion-exchange Chromatography of Uricase

Preparative ion-exchange chromatography was performed on a Fast Protein Liquid Chromatography (FPLC) apparatus (Amersham Pharmacia, Piscataway, N.J.). The Mono Q column (1×10 cm, Amersham Pharmacia) was eluted with a gradient of 50 mM sodium carbonate, pH 10.3, 0.1 M NaCl (Buffer A) to 50 mM sodium carbonate, pH 10.3, 0.6 M NaCl (Buffer B) at a flow rate of 0.5 ml/min, except that the sample was loaded at a lower flow-rate. This technique was used to fractionate 25 mL of a solution of PKS uricase (pH 10.3). PKS uricase was obtained from Bio-Technology General Limited (Rehovot, Israel). The latter is recombinant porcine uricase in which one residue of lysine (K) and one residue of serine (S) have replaced one residue of arginine and one residue of threonine, respectively, in the parental porcine sequence (Lee et al. (1988) Science 239:1288–1291; Wu et al. (1989) *Proc. Natl. Acad. Sci. U. S. A.* 86::9412–9416). After the sample was loaded, the column was washed with 100 mL of Buffer A. The peak of uricase began to elute at the end of a 31-mL linear gradient of 0 to 26% Buffer B. Most of the uricase was eluted isocratically by 7mL of buffer containing 26% Buffer B. The remainder of the recovered uricase was eluted by a linear 89-mL gradient of 26% to 100% buffer B. Fractions of 4 mL or 6 mL were collected. Aliquots of Fractions #4–11 were assayed for uricase, total protein and NaCl concentration (FIG. 1) and were analyzed by size-exclusion high performance liquid chromatography (HPLC) as described in Example 2 (FIGS. 2 and 3). The remaining portions of Fractions #5–10 were coupled to PEG, as described in Example 3. Based on the results of the analyses in Example 2, the PEG conjugates of Fractions #5 and 6 were combined as the "Low-Salt Pool" and the PEG conjugates of Fractions #7–10 were combined as the "High-Salt Pool," as indicated in FIG. 1.

EXAMPLE 2

Size-exclusion Chromatography of Uricase Monitored by Light Scattering and Ultraviolet Absorbance

Size-exclusion HPLC was performed at room temperature on a Superdex 200 column (1×30 cm, Amersham Pharmacia Biotech) on unfractionated PKS uricase and on selected fractions from the preparative Mono Q chromatography of PKS uricase of Example 1. The eluate from the absorbance monitor (UV 2000) of the Thermo Separations HPLC (Sunnyvale, Calif.) was analyzed by light scattering at 90° to the incident light, using a MiniDawn detector from Wyatt Technologies (Santa Barbara, Calif.).

The results shown in FIGS. 2–4 illustrate the resolution among the tetramer, octamer and larger aggregates of the uricase subunit and the different proportions of the signals detected from these forms of uricase in the various samples. Unlike the absorbance signal, which is directly proportional to the concentration, the light scattering signal is proportional to the product of the concentration times the size of the light scattering unit. The resultant sensitivity of the light scattering detector to very small amounts of highly aggregated uricase revealed the presence of the largest aggregates, which are eluted at or near the void volume (approximately 7 mL).

EXAMPLE 3

Synthesis of PEG-uricase Conjugates

Unfractionated PKS uricase (from Bio-Technology General Limited) and the uricase in fractions from the Mono Q column of Example 1 were coupled to 10-kDa PEG using the p-nitrophenyl carbonate derivative of PEG (NPC-PEG) obtained from Shearwater Polymers (Huntsville, Ala.). The preparation of NPC-PEG from PEG using phenylchloroformates has been described in several reports (e.g. Veronese, FM, et al., (1985) *Appl Biochem Biotechnol* 11:141–152; Kito, M, et al., (1996) *J Clin Biochem Nutr* 21:101–111) and NPC-PEG has been used for the synthesis of PEG-protein conjugates by previous investigators including the present inventors (e.g. Veronese et al., supra; Sherman M R, et al., in J M Harris, et al., (Eds.) *Poly(ethylene glycol) Chemistry and Biological Applications ACS Symposium Series* 680 (pp. 155–1706 Washington, D.C.: American Chemical Society). The number of strands of 10-kDa PEG coupled to each subunit of uricase was determined to be six by the method described by Kunitani, M, et al., (1991) *J Chromatogr* 588:125–137.

EXAMPLE 4

In Vivo Serum Persistence and immunogenicity of Uricase and PEG-uricase

PEG conjugates of recombinant mammalian uricases, prepared according to the method of Example 3, were adjusted to 1 mg protein/mL in phosphate-buffered saline (PBS), pH 7.4, for injection. Samples were frozen and stored until analyzed or injected. Samples were warmed to 37° C. for up to 1 hour prior to injection into groups of eight BALB/c female mice. The groups of mice had mean weights in the range of 18–22 g at the start of the studies.

The weights of all mice were monitored and evidence of adverse reactions to the injections or other evidence of ill health was recorded. Twenty-four hours after each of six weekly injections, the animals were anesthetized with ketamine and 100–200 μL of blood was obtained retro-orbitally, except at sacrifice (exsanguination), when a larger volume was collected. Serum was prepared from blood that had clotted for between 4 and 32 hours at 2–8° C. Sera were stored at −20° C. Sera were analyzed for uricolytic activity as described in Example 5 and analyzed for antibodies against uricases as described in Example 6.

EXAMPLE 5

Uricolytic Activity Assays of PEG-uricase in Sera from Mice Injected with PEG-uricase

An activity assay based on ultraviolet light absorbance (UV assay) was performed with 100 μM uric acid as the substrate in 200 mM sodium borate, pH 9.2, in a microplate adaptation of the method of I. Fridovich (*J Biol Chem.* (1965) 240:2491–2494). The decrease in absorbance at 292 nm was monitored for 15 minutes at room temperature in a 96-well plate with a UV-transparent bottom (Costar, Coming, N.Y.), using a SpectraMAX 250 microplate reader from Molecular Devices (Sunnyvale, Calif.). The data were analyzed by finding the maximum slope (in milli-absorbance units per minute) of absorbance measurements made during the interval while between 10 and 40% of the substrate was oxidized. Results obtained with this assay are illustrated in FIGS. 1 and 5.

The mean half-life in sera of mice injected for the first time with PKS uricase coupled to six strands of 10-kDa PEG per subunit (6×10-kDa PEG PKS) was 29±4 hours, based on data from sera obtained 24 and 72 hours after the injection.

In separate experiments, it was established that the detectable uricolytic activity in the sera of mice injected with PEG-uricase declines during storage at −20° C. and that maximal recovery of this activity is obtained by a 4-hour incubation at 37° prior to assay. FIG. 5 shows that the recovery of uricolytic activity after repeated weekly injections of 6×10-kDa PEG PKS uricase was greatest when the enzyme was purified by Mono Q column chromatography, as in Example 1, prior to PEGylation according to the method of Example 3. Recovery was highest after the injection of conjugates prepared from the high-salt eluate pool of Example 1 (see FIG. 1), which has the smallest content of the very large aggregates (see the light scattering profiles of Fractions 7–10 in FIG. 3). Intermediate recovery was obtained with conjugates prepared from the low-salt eluate pool from the Mono Q column of Example 1, and the poorest recovery was obtained with conjugates made from unfractionated PKS uricase, which has the highest content of very large aggregates (see FIG. 2). The same order of relative activities recovered in sera after repeated injections (high salt pool>low salt pool>unfractionated uricase) was observed regardless of whether the UV assay described above or a colorimetric assay adapted from P. Fossati et al. (*J. Clin Chem* (1980) 26:227–231), was used and regardless of whether the sera were incubated at 37° C. before they were assayed.

EXAMPLE 6

Enzyme-linked Immunosorbent Assay (ELISA) of Sera from Mice Injected with PEG-uricase

Non-competitive ELISA analyses were performed with porcine uricase bound to 96-well Immulon 2 plates (Dynex Technologies, from VWR Scientific, San Francisco, CA). The primary antisera were from mice injected with uricase or 6×10-kDa PEG conjugates prepared according to the method of Example 3. The secondary antibody was goat anti-mouse IgG coupled to horseradish peroxidase (Calbiochem-Novabiochem #401 253, La Jolla, Calif.) and the substrate was o-phenylenediamine dihydrochloride (Sigma P-9187, St. Louis, Mo.), as described by B. Porstmann et al. (*J Clin. Chem. Clin. Biochem.* (1981) 19:435–440).

FIG. 6 illustrates the results of the non-competitive ELISA analyses. The results demonstrate that the 6×10-kDa PEG PKS uricase synthesized according to the method of Example 3 from the high-salt eluate from the Mono Q column of Example 1 (shown in FIG. 1) did not produce detectable immune responses in any of the eight mice that

received weekly injections for six weeks. A few mice injected with conjugates prepared from unfractionated PKS uricase according to the method of Example 3 showed low but detectable immune responses. The highest incidence of immune responses was in mice injected with conjugates prepared according to the method of Example 3 from the low-salt eluate pool from the Mono Q column of Example 1.

Without the benefit of the light scattering detector for the size-exclusion HPLC analyses, as described in Example 2, it would not have been apparent that the presence of the largest aggregates, not of the octameric form of uricase, is associated with progressively decreased recovery of PEG-uricase conjugates after repeated injections, as observed in Example 5 (FIG. 5) and with an increase in immunogenicity in BALB/c mice, as observed in Example 6 (FIG. 6). These results have important implications for the specifications of the uricase used as a starting material for the production of PEG-uricase for clinical use.

Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it is readily apparent to those of ordinary skill in the art in light of the teachings of this invention that certain changes and modifications may be made thereto without departing from the spirit and scope of that which is described and claimed.

SEQUENCE LISTING

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<212> TYPE: PRT
<213> ORGANISM: Sus scrofa

<400> SEQUENCE: 1

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Arg Asp Gly Lys Tyr His Ser Ile Lys Glu Val Ala Thr Ser Val Gln
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Leu Thr Leu Ser Ser Lys Lys Asp Tyr Leu His Gly Asp Asn Ser Asp
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Val Ile Pro Thr Asp Thr Ile Lys Asn Thr Val Asn Val Leu Ala Lys
65                  70                  75                  80

Phe Lys Gly Ile Lys Ser Ile Glu Thr Phe Ala Val Thr Ile Cys Glu
                85                  90                  95

His Phe Leu Ser Ser Phe Lys His Val Ile Arg Ala Gln Val Tyr Val
            100                 105                 110

Glu Glu Val Pro Trp Lys Arg Phe Glu Lys Asn Gly Val Lys His Val
        115                 120                 125

His Ala Phe Ile Tyr Thr Pro Thr Gly Thr His Phe Cys Glu Val Glu
    130                 135                 140

Gln Ile Arg Asn Gly Pro Pro Val Ile His Ser Gly Ile Lys Asp Leu
145                 150                 155                 160

Lys Val Leu Lys Thr Thr Gln Ser Gly Phe Glu Gly Phe Ile Lys Asp
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Gln Phe Thr Thr Leu Pro Glu Val Lys Asp Arg Cys Phe Ala Thr Gln
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        195                 200                 205

Ala Thr Trp Asp Thr Val Arg Ser Ile Val Leu Gln Lys Phe Ala Gly
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Pro Tyr Asp Lys Gly Glu Tyr Ser Pro Ser Val Gln Lys Thr Leu Tyr
225                 230                 235                 240

Asp Ile Gln Val Leu Thr Leu Gly Gln Val Pro Glu Ile Glu Asp Met
                245                 250                 255

Glu Ile Ser Leu Pro Asn Ile His Tyr Leu Asn Ile Asp Met Ser Lys
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-continued

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            260                 265                 270

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Arg Asp Gly Lys Tyr His Ser Ile Lys Glu Val Ala Thr Ser Val Gln
        35                  40                  45

Leu Thr Leu Ser Ser Lys Lys Asp Tyr Leu His Gly Asp Asn Ser Asp
    50                  55                  60

Ile Ile Pro Thr Asp Thr Ile Lys Asn Thr Val His Val Leu Ala Lys
65                  70                  75                  80

Phe Lys Gly Ile Lys Ser Ile Glu Ala Phe Gly Val Asn Ile Cys Glu
                85                  90                  95

Tyr Phe Leu Ser Ser Phe Asn His Val Ile Arg Ala Gln Val Tyr Val
            100                 105                 110

Glu Glu Ile Pro Trp Lys Arg Leu Glu Lys Asn Gly Val Lys His Val
        115                 120                 125

His Ala Phe Ile His Thr Pro Thr Gly Thr His Phe Cys Glu Val Glu
    130                 135                 140

Gln Leu Arg Ser Gly Pro Pro Val Ile His Ser Gly Ile Lys Asp Leu
145                 150                 155                 160

Lys Val Leu Lys Thr Thr Gln Ser Gly Phe Glu Gly Phe Ile Lys Asp
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Gln Phe Thr Thr Lys Pro Glu Val Lys Asp Arg Cys Phe Ala Thr Gln
            180                 185                 190

Val Tyr Cys Lys Trp Arg Tyr His Gln Cys Arg Asp Val Asp Phe Glu
        195                 200                 205

Ala Thr Trp Gly Thr Ile Arg Asp Leu Val Leu Glu Lys Phe Ala Gly
    210                 215                 220

Pro Tyr Asp Lys Gly Glu Tyr Ser Pro Ser Val Gln Lys Thr Leu Tyr
225                 230                 235                 240

Asp Ile Gln Val Leu Ser Leu Ser Arg Val Pro Glu Ile Glu Asp Met
                245                 250                 255

Glu Ile Ser Leu Pro Asn Ile His Tyr Phe Asn Ile Asp Met Ser Lys
            260                 265                 270

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Val Arg Thr Gly Tyr Gly Lys Asp Met Ile Lys Val Leu His Ile Gln
            20                  25                  30

Arg Asp Gly Lys Tyr His Ser Ile Lys Glu Val Ala Thr Ser Val Gln
        35                  40                  45

Leu Thr Leu Ser Ser Lys Lys Asp Tyr Leu His Gly Asp Asn Ser Asp
    50                  55                  60

Val Ile Pro Thr Asp Thr Ile Lys Asn Thr Val Asn Val Leu Ala Lys
65                  70                  75                  80

Phe Lys Gly Ile Lys Ser Ile Glu Thr Phe Ala Val Thr Ile Cys Glu
                85                  90                  95

His Phe Leu Ser Ser Phe Lys His Val Ile Arg Ala Gln Val Tyr Val
            100                 105                 110

Glu Glu Val Pro Trp Lys Arg Phe Glu Lys Asn Gly Val Lys His Val
        115                 120                 125

His Ala Phe Ile Tyr Thr Pro Thr Gly Thr His Phe Cys Glu Val Glu
    130                 135                 140

Gln Ile Arg Asn Gly Pro Pro Val Ile His Ser Gly Ile Lys Asp Leu
145                 150                 155                 160

Lys Val Leu Lys Thr Thr Gln Ser Gly Phe Glu Gly Phe Ile Lys Asp
                165                 170                 175

Gln Phe Thr Thr Leu Pro Glu Val Lys Asp Arg Cys Phe Ala Thr Gln
            180                 185                 190

Val Tyr Cys Lys Trp Arg Tyr His Gln Gly Arg Asp Val Asp Phe Glu
        195                 200                 205

Ala Thr Trp Asp Thr Val Arg Ser Ile Val Leu Gln Lys Phe Ala Gly
    210                 215                 220

Pro Tyr Asp Lys Gly Glu Tyr Ser Pro Ser Val Gln Lys Thr Leu Tyr
225                 230                 235                 240

Asp Ile Gln Val Leu Thr Leu Gly Gln Val Pro Glu Ile Glu Asp Met
                245                 250                 255

Glu Ile Ser Leu Pro Asn Ile His Tyr Leu Asn Ile Asp Met Ser Lys
            260                 265                 270

Met Gly Leu Ile Asn Lys Glu Glu Val Leu Leu Pro Leu Asp Asn Pro
        275                 280                 285

Tyr Gly Lys Ile Thr Gly Thr Val Lys Arg Lys Leu Ser Ser Arg Leu
    290                 295                 300
```

What is claimed is:

1. Purified urate oxidase (uricase) that contains no more than about 2% of aggregates larger than octamers, wherein greater than about 20% of said uricase is in the tetrameric or octameric form.

2. The uricase of claim 1, wherein the uricase is mammalian uricase.

3. The uricase of claim 2, wherein the uricase is porcine liver, bovine liver or ovine liver uricase.

4. The uricase of claim 1, wherein the uricase is recombinant.

5. The uricase of claim 4, wherein the uricase has the sequence of porcine, bovine, ovine or baboon liver uricase.

6. The uricase of claim 4, wherein the uricase is chimeric.

7. The uricase of claim 6, wherein the chimeric uricase contains portions of porcine liver and baboon liver uricase.

8. The uricase of claim 7, wherein the chimeric uricase is porcine uricase in which arginine residue 291 of SEQ ID NO:2 has been replaced by lysine (R291 K) and threonine residue 301 of SEQ ID NO:2 has been replaced by serine (T301 S) (PKS uricase).

9. The uricase of claim 4, wherein the uricase has the sequence as set forth in SEQ ID NO:2, wherein tyrosine 97 has been replaced by histidine.

10. The uricase of claim 1, wherein the uricase is a fungal or microbial uricase.

11. The uricase of claim 10, wherein the fungal or microbial uricase is isolated from *Aspergillus flavus, Arthrobacter globiformis*, Bacillus sp. or *Candida utilis*, or is a recombinant enzyme having the sequence of one of said uricases.

12. The uricase of claim 1, wherein the uricase is an invertebrate uricase.

13. The uricase of claim 12, wherein the invertebrate uricase is isolated from *Drosophila melanogaster* or *Drosophila pseudoobscura*, or is a recombinant enzyme having the sequence of one of said uricases.

14. The uricase of claim 1, wherein the uricase is a plant uricase.

15. The uricase of claim 14, wherein the plant uricase is isolated from root nodules of *Glycine max* or is a recombinant enzyme having the sequence of said uricase.

16. A uricase conjugate comprising the uricase of claim 1 conjugated to poly(ethylene glycol) or poly(ethylene oxide).

17. The uricase conjugate of claim 16, wherein said poly(ethylene glycol) is monomethoxy poly(ethylene glycol).

18. The uricase conjugate of claim 16, wherein said uricase is conjugated to said poly(ethylene glycol) or poly (ethylene oxide) via a linkage selected from the group consisting of urethane (carbamate), secondary amine and amide.

19. The uricase conjugate of claim 16, wherein said poly(ethylene glycol) or poly(ethylene oxide) has a molecular weight between about 5 kDa and 30 kDa.

20. The uricase conjugate of claim 19, wherein said poly(ethylene glycol) or poly(ethylene oxide) has a molecular weight between about 10 kDa and 20 kDa.

21. The uricase conjugate of claim 16, wherein the average number of strands of said poly(ethylene glycol) or poly(ethylene oxide) is between about 2 and 12 per uricase subunit.

22. The uricase conjugate of claim 21, wherein the average number of strands of said poly(ethylene glycol) or poly(ethylene oxide) is between about 6 and 10 per uricase subunit.

23. The uricase conjugate of claim 22, wherein the average number of strands of said poly(ethylene glycol) or poly(ethylene oxide) is between about 7 and 9 per uricase subunit.

24. The uricase conjugate of claim 16, wherein the poly(ethylene glycol) or poly(ethylene oxide) is linear.

25. The uricase conjugate of claim 16, wherein the poly(ethylene glycol) or poly(ethylene oxide) is branched.

26. A pharmaceutical composition for lowering uric acid levels in a body fluid or tissue, comprising the conjugate of claim 16 and a pharmaceutically acceptable carrier.

27. The pharmaceutical composition of claim 26, wherein said composition is stabilized by lyophilization and dissolves upon reconstitution to provide solutions suitable for parenteral administration.

28. A purified fragment of uricase that contains no more than about 2% of aggregates larger than octamers, wherein said fragment is a recombinant uricase that has been truncated at the amino terminus, at the carboxyl terminus, or at both the amino and carboxyl termini, and wherein greater than about 20% of said truncated uricase is in the tetrameric or octameric form.

29. The purified uricase of claim 1, wherein about 98% to about 100% of said uricase is in the tetrameric or octameric form.

30. Isolated uricase prepared by a method comprising separating uricase aggregates larger than octamers from uricase tetramers and octamers and excluding such aggregates from the isolated uricase, wherein about 98% to about 100% of said uricase is in the tetrameric or octameric form.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,783,965 B1
APPLICATION NO. : 09/501730
DATED : August 31, 2004
INVENTOR(S) : Sherman et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the Title page, 1st column, please delete Item (75), "Merry R. Sherman, San Carlos, CA (US); Mark G.P. Saifer, San Carlos, CA (US); L. David Williams, Fremont, CA (US);" and insert therein -- Merry R. Sherman, San Carlos, CA (US); Mark G.P. Saifer, San Carlos, CA (US); L. David Williams, Fremont, CA (US); Michael S. Hershfield, Durham, NC (US); Susan J. Kelly, Chapel Hill, NC (US);--

and

In column 18, Line 52-57 please delete claim 8, "The uricase of claim 7, wherein the chimeric uricase is porcine uricase in which arginine residue 291 of SEQ ID NO:2 has been replaced by lysine (R291 K) and threonine residue 301 of SEQ ID NO:2 has been replaced by serine (T301 S) (PKS uricase)." and insert therein --The uricase of claim 7, wherein the chimeric uricase is porcine uricase in which arginine residue 291 of SEQ ID NO:1 has been replaced by lysine (R291 K) and threonine residue 301 of SEQ ID NO:1 has been replaced by serine (T301 S) (PKS uricase). --

Signed and Sealed this

Nineteenth Day of December, 2006

JON W. DUDAS
Director of the United States Patent and Trademark Office

Disclaimer

6,783,965 — Merry R. Sherman, San Carlos, CA (US); Mark G. P. Saifer, San Carlos, CA (US); and L. David Williams, Fremont, CA (US). AGGREGATE-FREE URATE OXIDASE FOR PREPARATION OF NON-IMMUNOGENIC POLYMER CONJUGATES. Patent dated August 31, 2004. Disclaimer filed August 05, 2008, by the assignee, Mountain View Pharmaceuticals, Inc.

The term of this patent should not extend beyond the expiration date of Patent No. 6,576,235.

(Official Gazette November 25, 2008)

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,783,965 B1
APPLICATION NO. : 09/501730
DATED : August 31, 2004
INVENTOR(S) : Sherman et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the Title page of the patent, please replace exemplary drawing FIG. 1 with corrected FIG. 1.

Also, please replace FIG. 1 and FIG. 5 with corrected replacement figures attached herein.

Signed and Sealed this

First Day of September, 2009

David J. Kappos

David J. Kappos
Director of the United States Patent and Trademark Office

(12) **United States Patent**
Sherman et al.

(10) **Patent No.: US 6,783,965 B1**
(45) **Date of Patent: *Aug. 31, 2004**

(54) **AGGREGATE-FREE URATE OXIDASE FOR PREPARATION OF NON-IMMUNOGENIC POLYMER CONJUGATES**

(75) Inventors: **Merry R. Sherman**, San Carlos, CA (US); **Mark G. P. Saifer**, San Carlos, CA (US); **L. David Williams**, Fremont, CA (US)

(73) Assignee: **Mountain View Pharmaceuticals, Inc.**, Menlo Park, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **09/501,730**

(22) Filed: **Feb. 10, 2000**

(51) **Int. Cl.**[7] **C12N 9/04**; C12N 15/00; A61K 38/44; C07K 1/00; C07H 21/04

(52) **U.S. Cl.** **435/190**; 435/191; 435/440; 424/94.4; 536/23.2; 530/350

(58) **Field of Search** 435/190, 191, 435/440, 170; 424/94.4, 94.6; 536/23.2; 530/350, 413

(56) **References Cited**

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Caliceti et al. Biopharmaceutical properties of uricase conjugated to neutral and amphiphilic polymer. Bioconjugate Chem. 10, 638–646. (1999).*

(List continued on next page.)

Primary Examiner—Ponnathapu Achutamurthy
Assistant Examiner—Yong Pak
(74) *Attorney, Agent, or Firm*—Sterne, Kessler, Goldstein & Fox P.L.L.C.

(57) **ABSTRACT**

A naturally occurring or recombinant protein, especially a mutein of porcine urate oxidase (uricase), that is essentially free of large aggregates can be rendered substantially non-immunogenic by conjugation with a sufficiently small number of strands of polymer such that the bioactivity of the protein is essentially retained in the conjugate. Such conjugates are unusually well suited for treatment of chronic conditions because they are less likely to induce the formation of antibodies and/or accelerated clearance than are similar conjugates prepared from protein preparations containing traces of large aggregates.

30 Claims, 6 Drawing Sheets

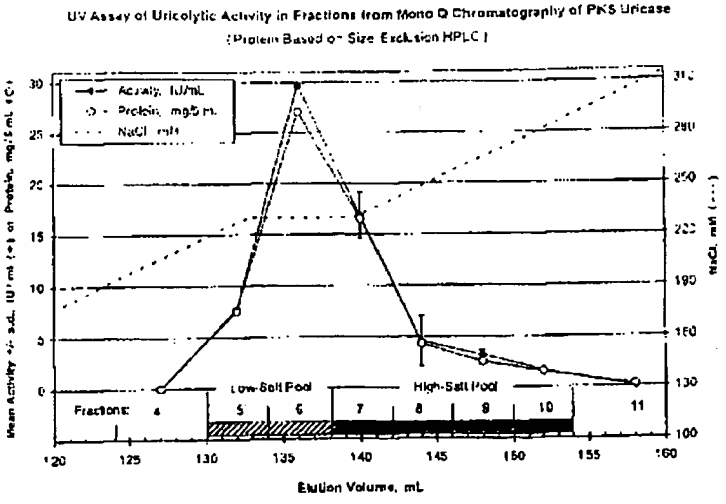


FIG. 1

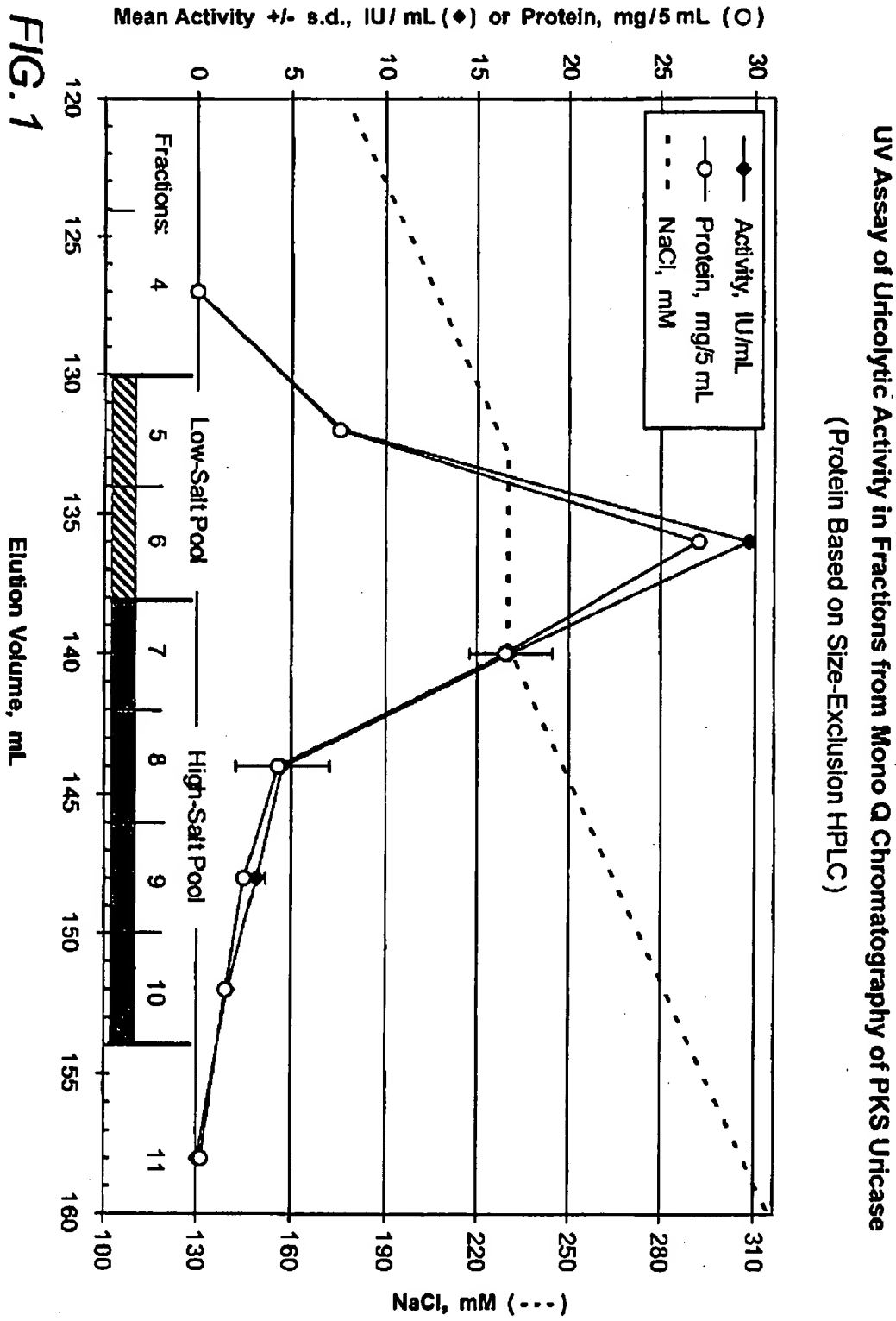
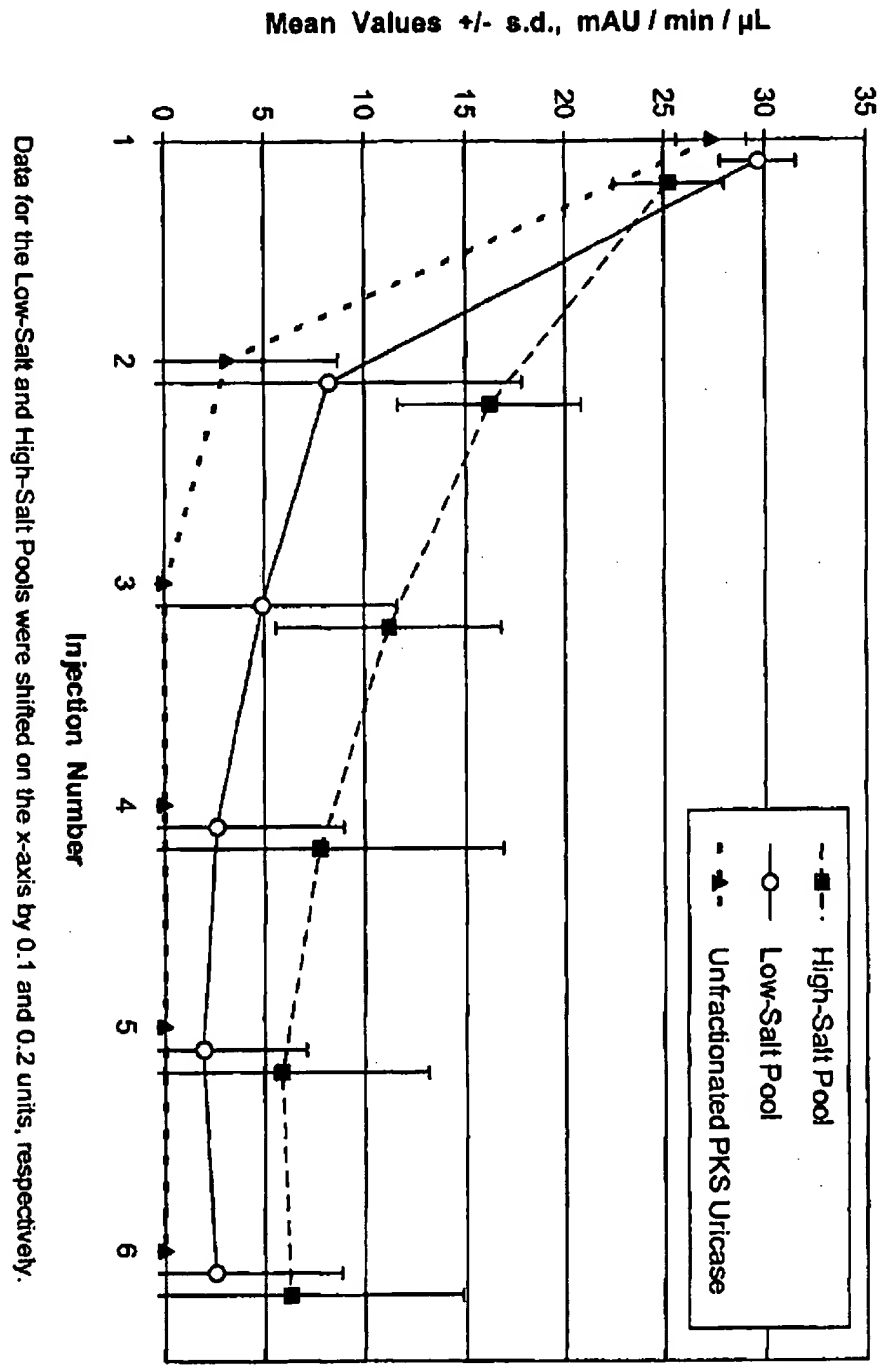

UV Assay of Uricolytic Activity in Fractions from Mono Q Chromatography of PKS Uricase
(Protein Based on Size-Exclusion HPLC)
Mean Activity +/- s.d., IU/mL (◆) or Protein, mg/5 mL (○)
Activity, IU/mL
Protein, mg/5 mL
NaCl, mM
Fractions: 4 5 6 7 8 9 10 11
Low-Salt Pool
High-Salt Pool
Elution Volume, mL
NaCl, mM (- - -)

FIG. 5

UV Uricase Assays of Sera from Mice Injected with 6 x 10-kDa PEG Conjugates of PKS Uricase or of Pools from Mono Q Column Fractions
(Mice Were Bled 24 Hours after Each Weekly Injection.)



Data for the Low-Salt and High-Salt Pools were shifted on the x-axis by 0.1 and 0.2 units, respectively.

EXHIBIT 6

PTO/SB/26 (08-03)
Approved for use through 07/31/2006. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

TERMINAL DISCLAIMER TO OBVIATE A DOUBLE PATENTING REJECTION OVER A PRIOR PATENT	Docket Number (Optional) 2057.0080000/BJD

In re Application of: SHERMAN *et al.*

Application No.: 09/501,730

Filed: February 10, 2000

For: **Aggregate-Free Urate Oxidase for Preparation of Non-Immunogenic Polymer Conjugates**

The owner*, Mountain View Pharmaceuticals, Inc., of 100 percent interest in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term defined in 35 U.S.C. 154 and 173, as presently shortened by any terminal disclaimer, of prior Patent No. 6,576,235. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the prior patent are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the owner does not disclaim the terminal part of any patent granted on the instant application that would extend to the expiration date of the full statutory term as defined in 35 U.S.C. 154 and 173 of the prior patent, as presently shortened by any terminal disclaimer, in the event that it later: expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of competent jurisdiction, is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321, has all claims canceled by a reexamination certificate, is reissued, or is in any manner terminated prior to the expiration of its full statutory term as presently shortened by any terminal disclaimer.

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

2. ☒ The undersigned is an attorney or agent of record.

Signature Date: Dec. 4, 2003

Brian J. Del Buono, Reg. No. 42,473
Typed or printed name

202-371-2600
Telephone Number

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*Statement under 37 CFR 3.73(b) is required if terminal disclaimer is signed by the assignee (owner). Form PTO/SB/96 may be used for making this statement. See MPEP § 324.

EXHIBIT 7

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent of:	Confirmation No.: 4303
Sherman *et al.*	Art Unit: 1652
U.S. Patent No. 6,783,965	Examiner: Pak, Yong D.
Issued: August 31, 2004	Atty. Docket: 2057.0080000/BJD/SAC
For: **Aggregate-Free Urate Oxidase for Preparation of Non-immunogenic Polymer Conjugates**	

Statutory Terminal Disclaimer Under 35 U.S.C. § 253 and 37 C.F.R. § 1.321(a)

Commissioner for Patents
Washington, D.C. 20231

Sir:

During prosecution of U.S. Appl. No. 09/501,730 which resulted in the issuance of the above-captioned patent, a Terminal Disclaimer was filed by Mountain View Pharmaceuticals, Inc. on December 4, 2003. Subsequent to execution of the Terminal Disclaimer and issuance of the above-captioned patent, inventorship was amended pursuant to 37 C.F.R. § 1.324(a). As a result, the above-captioned patent is now co-owned by Mountain View Pharmaceuticals, Inc. and Duke University. In view of the corrected inventorship, co-owner Duke University encloses an executed Terminal Disclaimer that also is executed by co-owner Mountain View Pharmaceuticals, Inc. Thus, so that the record of the above-captioned patent is clear, the co-owners hereby provide a joint Terminal Disclaimer.

Mountain View Pharmaceuticals, Inc. and Duke University represent that they are the owners of the entire right, title, and interest of U.S. Application No. 09/501,730, filed on February 10, 2000, and U.S. Patent No. 6,783,965 that issued therefrom, by virtue of:

(a) an Assignment from Merry R. Sherman, Mark G.P. Saifer and L. David Williams to Mountain View Pharmaceuticals, Inc. executed on April 26, 2000, recorded on May 22, 2000, at Reel 010836, Frame 0572; and

(b) an Assignment from Michael S. Hershfield and Susan J. Kelly to Duke University executed on May 16, 2006 and May 17, 2006 respectively, recorded on May 24, 2006, at Reel 017663, Frame 0313.

Establishing Right of Assignee to Take Action Under 37 C.F.R. § 3.73(b)

A Statement Under 37 C.F.R. § 3.73(b) establishing the right of the assignee to take action, with regard to the above-identified application and patent was filed for Mountain View Pharmaceuticals, Inc. on May 24, 2006. Additionally, a Statement Under 37 C.F.R. § 3.73(b) establishing the right of the assignee to take action, with regard to the above-identified application and patent, was also filed in the above-captioned matter for Duke University on May 24, 2006.

Terminal Disclaimer

Mountain View Pharmaceuticals, Inc. and Duke University, hereby disclaim, except as provided below, the terminal part of the statutory term of the above-captioned patent which would extend beyond the expiration date of the full statutory term of prior patent No. 6,576,235 as the term of said prior patent is defined in 35 U.S.C. §§ 154 and 173, and as the term of said prior patent is presently shortened by any terminal disclaimer.

The co-owners hereby agree that the above-captioned patent shall be enforceable for and during such period that it and the prior patent are commonly owned. The co-owners further acknowledge that this disclaimer is to be binding upon the grantees, assignees, their successors or assigns.

In making the above disclaimer, the co-owners do not disclaim the terminal part of the term of the captioned patent that would extend to the expiration date of the full statutory term as defined in 35 U.S.C. §§ 154 and 173 of the **prior patent**, "as the term of said **prior patent** is presently shortened by any terminal disclaimer," in the event that said **prior patent** later:

expires for failure to pay a maintenance fee;
is held unenforceable;
is found invalid by a court of competent jurisdiction;
is statutorily disclaimed in whole or terminally disclaimed under 37 C.F.R. 1.321;
has all claims canceled by a reexamination certificate;
is reissued; or
is in any manner terminated prior to the expiration of its full statutory term as presently shortened by any terminal disclaimer.

The co-owners also do not disclaim any term of the above-captioned patent that is extended pursuant to 35 U.S.C. § 156.

In accordance with 37 C.F.R. § 1.321(a), this disclaimer is accompanied by the fee set forth in 37 C.F.R. § 1.20(d). We have read and understand 37 C.F.R. § 10.18(b).

For: Mountain View Pharmaceuticals, Inc.

Signature: Merry R. Sherman

Type or Print Name: Merry R. Sherman

Title: CEO and President

Date: July 17, 2008

For: Duke University

Signature:

Type or Print Name: Robert L. Taber, Ph.D.

Title: Vice Chancellor, Corporate & Venture Development

Date: 7/21/07

EXHIBIT 8

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,783,965 B1
APPLICATION NO. : 09/501730
DATED : August 31, 2004
INVENTOR(S) : Sherman et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

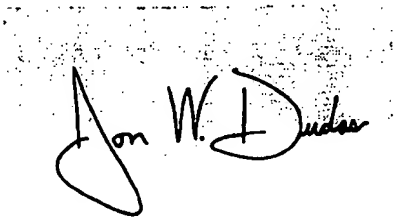
On the Title page, 1st column, please delete Item (75), "Merry R. Sherman, San Carlos, CA (US); Mark G.P. Saifer, San Carlos, CA (US); L. David Williams, Fremont, CA (US);" and insert therein -- Merry R. Sherman, San Carlos, CA (US); Mark G.P. Saifer, San Carlos, CA (US); L. David Williams, Fremont, CA (US); Michael S. Hershfield, Durham, NC (US); Susan J. Kelly, Chapel Hill, NC (US);--

and

In column 18, Line 52-57 please delete claim 8, "The uricase of claim 7, wherein the chimeric uricase is porcine uricase in which arginine residue 291 of SEQ ID NO:2 has been replaced by lysine (R291 K) and threonine residue 301 of SEQ ID NO:2 has been replaced by serine (T301 S) (PKS uricase)." and insert therein --The uricase of claim 7, wherein the chimeric uricase is porcine uricase in which arginine residue 291 of SEQ ID NO:1 has been replaced by lysine (R291 K) and threonine residue 301 of SEQ ID NO:1 has been replaced by serine (T301 S) (PKS uricase). --

Signed and Sealed this

Nineteenth Day of December, 2006



JON W. DUDAS
Director of the United States Patent and Trademark Office

EXHIBIT 9

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,783,965 B1
APPLICATION NO. : 09/501730
DATED : August 31, 2004
INVENTOR(S) : Sherman et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the Title page of the patent, please replace exemplary drawing FIG. 1 with corrected FIG. 1.

Also, please replace FIG. 1 and FIG. 5 with corrected replacement figures attached herein.

Signed and Sealed this

First Day of September, 2009

David J. Kappos

David J. Kappos
Director of the United States Patent and Trademark Office

(12) **United States Patent**
Sherman et al.

(10) **Patent No.: US 6,783,965 B1**
(45) **Date of Patent: *Aug. 31, 2004**

(54) **AGGREGATE-FREE URATE OXIDASE FOR PREPARATION OF NON-IMMUNOGENIC POLYMER CONJUGATES**

(75) Inventors: **Merry R. Sherman**, San Carlos, CA (US); **Mark G. P. Saifer**, San Carlos, CA (US); **L. David Williams**, Fremont, CA (US)

(73) Assignee: **Mountain View Pharmaceuticals, Inc.**, Menlo Park, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **09/501,730**

(22) Filed: **Feb. 10, 2000**

(51) Int. Cl.[7] C12N 9/04; C12N 15/00; A61K 38/44; C07K 1/00; C07H 21/04

(52) U.S. Cl. 435/190; 435/191; 435/440; 424/94.4; 536/23.2; 530/350

(58) Field of Search 435/190, 191, 435/440, 170; 424/94.4, 94.6; 536/23.2; 530/350, 413

(56) **References Cited**

U.S. PATENT DOCUMENTS

3,616,231	A	10/1971	Bergmeyer et al.	
4,460,683	A	7/1984	Gloger et al.	
4,766,106	A	8/1988	Katre et al.	
4,847,325	A	7/1989	Shadle et al.	
4,917,888	A	4/1990	Katre et al.	
5,286,637	A	2/1994	Veronese et al.	435/183
5,382,518	A	1/1995	Caput et al.	
5,428,128	A	6/1995	Menni-Faltahi et al.	
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5,643,575	A	7/1997	Martinez et al.	424/194.1
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5,880,255	A	3/1999	Delgado et al.	
5,919,455	A	7/1999	Greenwald et al.	
6,376,235	B1 *	6/2003	Williams et al.	424/94.4
2002/0110319	A1 *	1/2002	Ansaldi et al.	530/387.1

FOREIGN PATENT DOCUMENTS

DE	279 486 A1	6/1990
JP	09154581	6/1997
WO	WO 94/19007	9/1994
WO	WO 00/07629	2/2000
WO	WO 00/08196	2/2000

OTHER PUBLICATIONS

Caliceti et al. Biopharmaceutical properties of uricase conjugated to neutral and amphiphilic polymer. Bioconjugate Chem. 10, 638–646. (1999).*

(List continued on next page.)

Primary Examiner—Ponnathapu Achutamurthy
Assistant Examiner—Yong Pak
(74) *Attorney, Agent, or Firm*—Sterne, Kessler, Goldstein & Fox P.L.L.C.

(57) **ABSTRACT**

A naturally occurring or recombinant protein, especially a mutein of porcine urate oxidase (uricase), that is essentially free of large aggregates can be rendered substantially non-immunogenic by conjugation with a sufficiently small number of strands of polymer such that the bioactivity of the protein is essentially retained in the conjugate. Such conjugates are unusually well suited for treatment of chronic conditions because they are less likely to induce the formation of antibodies and/or accelerated clearance than are similar conjugates prepared from protein preparations containing traces of large aggregates.

30 Claims, 6 Drawing Sheets

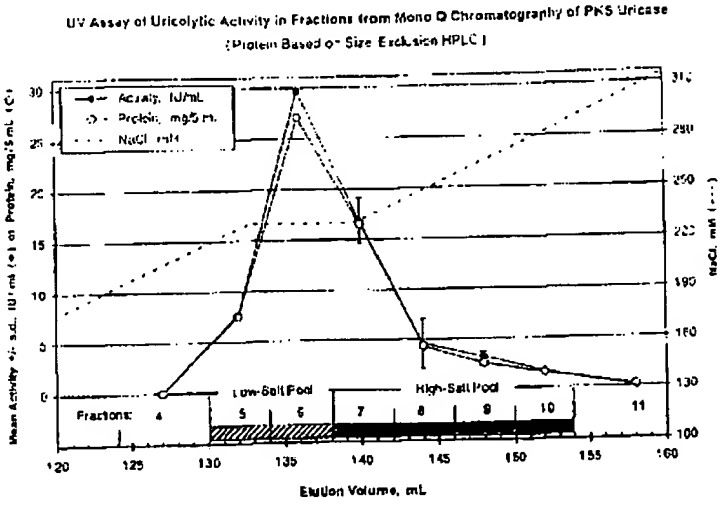


FIG. 1

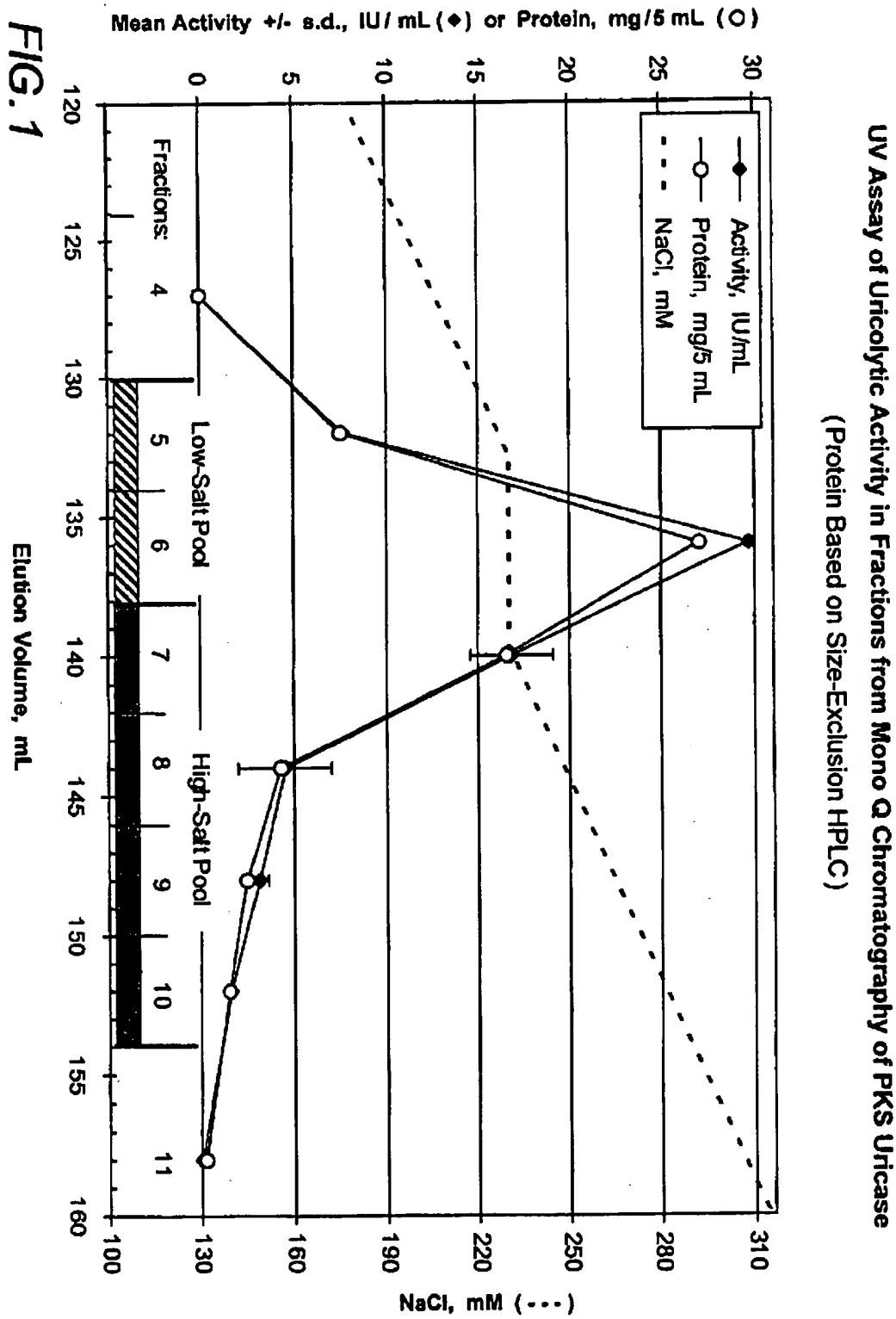
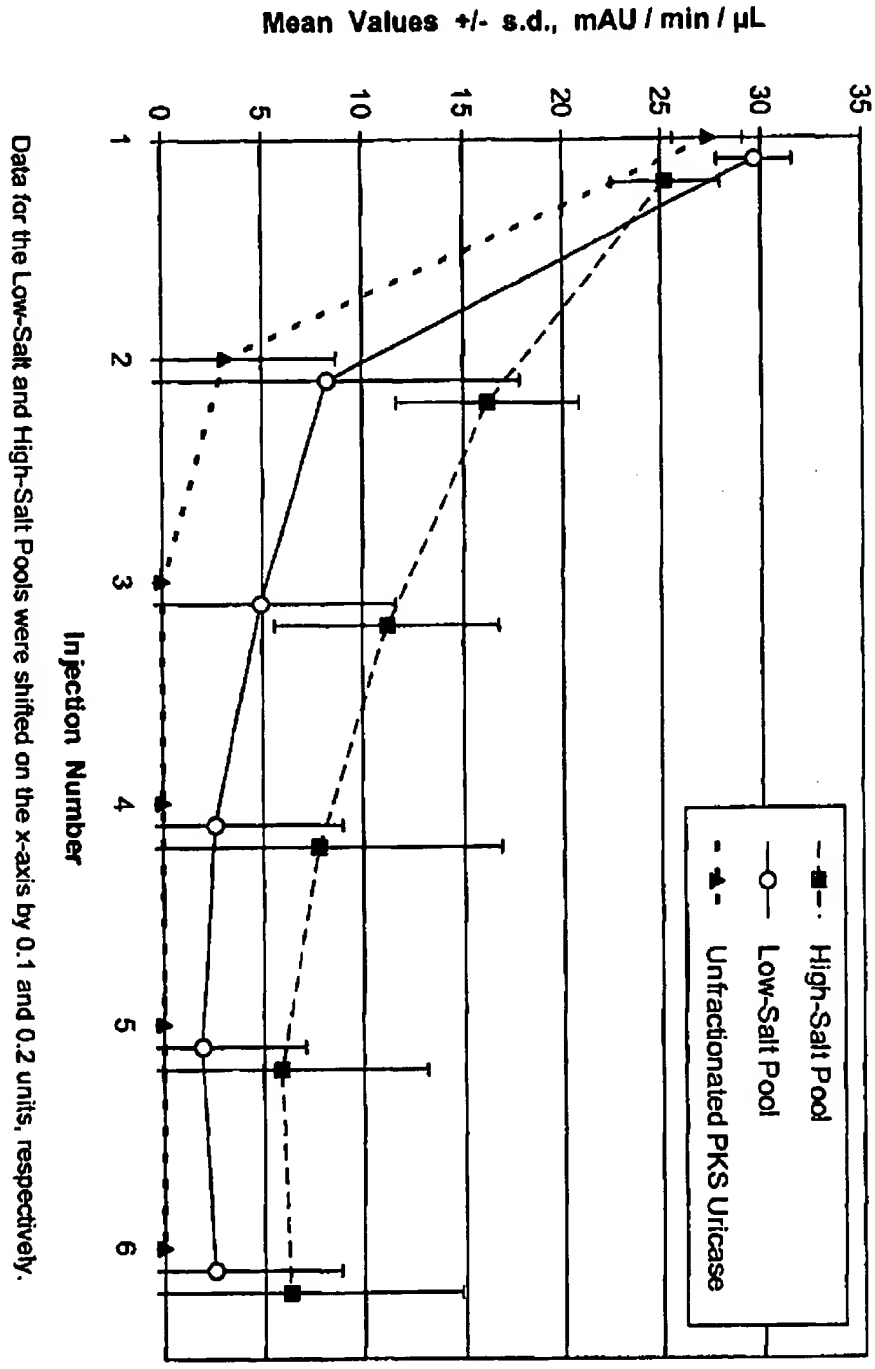

UV Assay of Uricolytic Activity in Fractions from Mono Q Chromatography of PKS Uricase
(Protein Based on Size-Exclusion HPLC)
Mean Activity +/- s.d., IU/mL (◆) or Protein, mg/5 mL (○)
Activity, IU/mL
Protein, mg/5 mL
NaCl, mM
Fractions: 4 5 6 7 8 9 10 11
Low-Salt Pool
High-Salt Pool
Elution Volume, mL
NaCl, mM (- - -)

FIG. 5

UV Unicase Assays of Sera from Mice Injected with 6 x 10-kDa PEG Conjugates of PKS Unicase or of Pools from Mono Q Column Fractions
(Mice Were Bled 24 Hours after Each Weekly Injection.)



Data for the Low-Salt and High-Salt Pools were shifted on the x-axis by 0.1 and 0.2 units, respectively.

EXHIBIT 10

Return To:

USPTO Home Page

Finance Online Shopping Page

United States Patent and Trademark Office

Maintenance Fee Statement

09/20/2010 11:10 AM EDT

Patent Number: 6783965

Customer Number: 26111

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C
1100 NEW YORK AVENUE, N.W.
WASHINGTON DC 20005

According to the records of the U.S.Patent and Trademark Office (USPTO), the maintenance fee and any necessary surcharge have been timely paid for the patent listed below. The "PYMT DATE" column indicates the payment date (i.e., the date the payment was filed).

The payment shown below is subject to actual collection. If the payment is refused or charged back by a financial institution, the payment will be void and the maintenance fee and any necessary surcharge unpaid.

Direct any questions about this statement to: Mail Stop M Correspondence, Director of the USPTO, P.O.Box 1450, Alexandria, VA 22313-1450.

PATENT NUMBER	FEE AMT	SUR-CHARGE	PYMT DATE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	SMALL ENTITY?	ATTY DKT NUMBER
6,783,965	$930.00	$0.00	02/14/08	09/501,730	08/31/04	02/10/00	04	NO	2057.0080000

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EXHIBIT 11

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
1401 Rockville Pike
Rockville MD 20852-1448

NOV 3 0 2001

Our Reference: BB-IND 10122

Bio-Technology General Corporation
Attention: Mr. Briti Kundu
Director, Regulatory Affairs
70 Wood Avenue South
Iselin, NJ 08830

Dear Mr. Kundu:

The Center for Biologics Evaluation and Research has received your **Investigational New Drug Application (IND)**. The following product name and BB-IND number have been assigned to this application. They serve only to identify it and do not imply that this Center either endorses or does not endorse your application.

BB-IND #: 10122

SPONSOR: Bio-Technology General Corporation

PRODUCT NAME: Uricase (recombinant, E coli, Bio-Technology General Corp.), PEG Conjugate

DATE OF SUBMISSION: November 15, 2001

DATE OF RECEIPT: November 19, 2001

This BB-IND number should be used to identify all future correspondence and submissions, as well as telephone inquiries concerning this IND. Please provide an **original and two copies of every submission to this file**. Please include three originals of all illustrations which do not reproduce well.

It is understood that studies in humans will not be initiated until 30 days after the date of receipt shown above. If this office notifies you, verbally or in writing, of serious deficiencies that require correction before human studies can begin, it is understood that you will continue to withhold such studies until you are notified that the material you have submitted to correct the deficiencies is satisfactory. If such a clinical hold is placed on this file, you will be notified in writing of the reasons for placing the IND on hold.

You are responsible for compliance with applicable portions of the Public Health Service Act, the Federal Food, Drug, and Cosmetic Act, and the Code of Federal Regulations (CFR). A copy of 21 CFR Part 312, pertaining to INDs, is enclosed. Copies of other pertinent regulations are available from this Center upon request.

The following points regarding obligations of an IND sponsor are included for your information only, and are not intended to be comprehensive.

Progress reports are required at intervals not exceeding one year and are due within 60 days of the anniversary of the date that the IND went into effect [21 CFR 312.33]. Any unexpected, fatal or immediately life-threatening reaction associated with use of this product must be reported to this Division by telephone or facsimile transmission no later than seven calendar days after initial receipt of the information. All serious, unexpected adverse experiences, as well as results from animal studies that suggest significant clinical risk, must be reported, in writing, to this Division and to all investigators within fifteen calendar days after initial receipt of this information [21 CFR 312.32].

Charging for an investigational product in a clinical trial under an IND is not permitted without the prior written approval of the FDA.

Prior to use of each new lot of the investigational biologic in clinical trials, please submit the lot number, the results of all tests performed on the lot, and the specifications when established (i.e., the range of acceptable results).

If not included in your submission, please provide copies of the consent forms for each clinical study. A copy of the requirements for and elements of informed consent are enclosed. Also, please provide documentation of the institutional review board approval(s) for each clinical study.

All laboratory or animal studies intended to support the safety of this product should be conducted in compliance with the regulations for "Good Laboratory Practice for Nonclinical Laboratory Studies" (21 CFR Part 58, copies available upon request). If such studies have not been conducted in compliance with these regulations, please provide a statement describing in detail all differences between the practices used and those required in the regulations.

Item 7a of form FDA 1571 requests that either an "environmental assessment," or a "claim for categorical exclusion" from the requirements for environmental assessment, be included in the IND. If you did not include a response to this item with your application, please submit one. See the enclosed information sheet for additional information on how these requirements may be addressed.

Telephone inquiries concerning this IND should be made directly to me at (301) 827-5101. Correspondence regarding this file should be addressed as follows:

Center for Biologics Evaluation and Research
Attn: Office of Therapeutics Research and Review
HFM-99, Room 200N
1401 Rockville Pike
Rockville, MD 20852-1448

If we have any comments after we have reviewed this submission, we will contact you.

Sincerely yours,

Jeanne M. Delasko

Jeanne M. Delasko, R.N., M.S.
Regulatory Project Manager
Division of Application Review and Policy
Office of Therapeutics
Research and Review
Center for Biologics
Evaluation and Research

Enclosures (3): 21 CFR Part 312
21 CFR 50.20, 50.25
Information sheet on 21 CFR 25.24

EXHIBIT 12

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

Our STN: BLA 125293/0

BLA ACKNOWLEDGEMENT

NOV 12 2008

Savient Pharmaceuticals, Inc.
One Tower Center Boulevard
14th Floor
East Brunswick, NJ 08816

Attention: Murad Husain
Vice President of Regulatory Affairs

Dear Mr. Husain:

We have received your biologics license application (BLA) submitted under section 351 of the Public Health Service Act (PHS Act) for the following:

Name of Biological Product: Pegloticase

Date of Application: October 31, 2008

Date of Receipt: October 31, 2008

Our Submission Tracking Number (STN): BL 125293/0

Proposed Use: Intravenous infusion intended for patients with treatment failure gout to control hyperuricemia and to manage the signs and symptoms of gout.

If you have not already done so, promptly submit the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action. The content of labeling must conform to the format and content requirements of revised 21 CFR 201.56-57.

We will notify you within 60 days of the receipt date if the application is sufficiently complete to permit a substantive review.

The BLA Submission Tracking Number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Therapeutic Biological Products Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission.

If you have any questions, call me at (301) 796-4029.

Sincerely,

Diana L. Walker, Ph.D.
Regulatory Project Manager
Division of Anesthesia, Analgesia
and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

EXHIBIT 13

PEG-URICASE®
PRE-IND/IND #10122

INDEX OF APPLICATION CORRESPONDENCES

Date	From	Info Type	Description
8/15/2000	BTG	Initial Submission	**Telephone Call Report** by B. Kundu to W. Aaronson FDA. Pre-IND Meeting Telephone Call
9/22/2000	BTG	Initial Submission	**Letter** to Dr. G. Jones, FDA: Request for a Pre-IND Meeting (Type B Meeting) PEG-Uricase from B. Kundu of BTG
9/22/2000	BTG	Initial Submission	**FAX** from BTGH to Lori Tull FDA - Request for a Meeting, attached copy of the pre-IND meeting request letter dated 9/22/00
9/26/2000	FDA	Initial Submission	**Telephone Call Report** by B. Glasscock FDA taken by M. Califre: Pre-IND Meeting Request
9/28/2000	BTG	Initial Submission	**Telephone Call Report** by B. Kundu to B. Glasscock of FDA. Scheduling of Pre-IND Conference call
10/2/2000	FDA	Initial Submission	**FAX** from B. Glasscock of FDA schedule confirmation of teleconferenc for Nove 13, 2000 to discuss the proposed preclinical and clincal development program
10/3/2000	BTG	Initial Submission	**Telephone Call Report** by M. Califre to FDA B. Glasscock. Confirmation of Receipt of FAX announcing Teleconference Date and Time
10/3/2000	FDA	CMC	**Telephone Call Report** Dr. B. Glasscock FDA to B. Kundu of BTG: FDA pre IND Meeting: CMC
10/12/2000	BTG	Initial Submission	**Letter** to Dr. G. Jones FDA: PEG-uricase Information Package for the Pre-IND Teleconference
11/9/2000	BTG	Initial Submission	**Fax** to B. Glasscock, CSO FDA PEG-uricase, Brief Outline of Presentations for Teleconference to take place today, November 13, 2000 (preIND meeting)
11/13/2000	BTG	Clinical	**Telephone Call Report** B. Kundu: Teleconference: Clinical Questions for the Phase I/II study
11/13/2000	BTG	Clinical	**Telephone Call Report**: Called by Norman barton: M. Califre, et al. Pre-IND teleconference to discuss the proposed preclinical and clinical development program (see attached meeting minutes)
11/13/2000	BTG	Initial Submission	**Letter** to Dr. G. Jones FDA: PEG-uricase…Outline of presentation materials for the Nov 13 2000 Pre-IND Teleconference
11/28/2000	FDA	Clinical	**Telephone Call Report J. Siegel: Returning a Devos' phone call to ask questions pertaining to PEG-uricase Clinical Program**
11/30/2000	BTG	Clinical	**Telephone Call Report:** Clinical Questions for the Phase I/II study; BTG will send an outline of the Phase I/II protocol and additional questions to Dr. Siegel
12/6/2000	FDA	Pharmacology/ Toxicology	**Telephone Call Report J. Siegel:** Response to pre-clinical questions asked by BTG during the telephone conference on 11/30/00
12/8/2000	FDA	Meeting Minutes	**Meeting Minutes**: Fax from FDA about Mtg Minutes Summary of November 13, 2000 meeting held to discuss the proposed Preclinical and Clinical Development Programs.
12/13/2000	BTG	Pharmacology/ Toxicology	**Outlines of Repeated-Dose Toxicity Studies and Phase I/II Clinical Protocol:** Letter to Glen Jones sent via FedEx
12/13/2000	BTG	Pharmacology/ Toxicology	**Outlines of Repeated-Dose Toxicity Studies and Phase I/II Clinical Protocol:** Fax to Jeffrey Siegel
12/13/2000	FDA	Meeting Minutes	**Meeting Minutes:** Receipt of FDA Summary of November 13, 2000 Meeting
12/19/2000	FDA	Correspondence	**Telephone Call Report:** Diane Sartor, Consumer Safety Technician, called to ask for the IND number for the 12/13/00 submission. B. Kundu informed her that we have not yet submitted the IND and the product is in the pre-IND development stage. B. Kundu no
1/4/2001	FDA	Pharmacology/ Toxicology	**Telephone Call Report:** Dr. Martin Green, FDA toxicology reviewer called and informed BTG that the protocol outline for the 56-day repeat dose rat and dog study, submitted on 12/13/00 was acceptable

PEG-URICASE®
PRE-IND/IND #10122

INDEX OF APPLICATION CORRESPONDENCES

Date	From	Info Type	Description
8/16/2001	BTG	Pharmacology/ Toxicology	**Telephone Call Report:** spoke to Dave(Martin) Green regarding the relevancy of a carcinogenicity study & the specifics of an animal reproduction study.
11/15/2001	BTG	New Protocol	**Serial No. 000: Original IND Application** (our Acknowledgement received 11/19/01)
11/30/2001	FDA	Correspondence	**Serial-000: BB-IND #10122** Acknowledgement Letter – 11/30/01
12/10/2001	BTG	Correspondence	**Serial-000:** Spoke to Jeannie Delasko (Marcy) re: Verify receipt of Puricase IND.
12/11/2001	FDA	Correspondence	**Telephone Call Report:** Dr. Jeffrey Siegel called to introduce himself. He also has a few questions regarding the protocol and would like to set-up a teleconference call for Tuesday, 12/12.
12/11/2001	BTG	Correspondence	**Serial-001: Gen'l Corres** - Notify FDA that Thomas, Marcy and Chris can be contacted regarding IND communications. (acknowledgement receipt 12/12)
12/12/2001	BTG	Correspondence	**E-Mail to Dr. Siegel:** Confirming conference call for Thursday, December 14 at 10am
12/13/2001	BTG	Clinical	**Teleconference to Discuss Questions on Protocol C0401.** Spoke w/Jeffrey Siegel
12/13/2001	BTG	Clinical	**Serial-002: Response to Request for Information** - Reference is made to the 12/13/01 teleconference call w/Dr. Siegel submitting draft copy of the consent form and a list of the protocol revisions.(acknowledgement receipt 12/14)
12/13/2001	BTG	Clinical	**FAX**: to Dr. Siegel "copy of the draft informed consent form for the protocol C0401 along with the list of protocol revisions – 12 pages
12/14/2001	FDA	Correspondence	**Telephone Call Report:** Dr. J. Siegel called to inform BTG that we can proceed with the clinical study C0401
12/18/2001	BTG	Correspondence	**Letter to Marlene Haffner** – Copy of letter to Orphan Products Development Division notifiying them of the filing of aBB- IND for Puricase (acknowledgement receipt 12/20/01 by Jeff Fritsch)
1/10/2002	FDA	Correspondence	**Telephone Call Report: w/Jeannie Delasko**: Schedule Teleconference to discuss proposed clinical reproduction studies with FDA preclinical reviewer
1/10/2002	BTG	Correspondence	**Telephone Call Report: w/Lauren Black** – Schedule Teleconference to discuss proposed preclinical reproduction studies with FDA preclinical reviewer
1/18/2002	FDA	Clinical	**FDA letter from Glen Jones :** Comments on IND submission: Agreement that C0401 study may proceed. Comments on CMC section of IND and request for additional CMC information during development, including submission of C of As for bulk drug substance and d
1/25/2002	BTG	Protocol Amendments	**S-003:** Submitted **Protocol Amendment No. One**, dated January 22, 2002 (receipt acknowledgement 1/28/02)
1/31/2002	BTG	Clinical	**S-004: Response to FDA Request for Information:** Submitted a copy of the approved informed consent form as well as documentation of IRB approval of the amended protocol. (our Acknowledgement received 02/02/02)
2/6/2002	BTG	Clinical	**S-005: Revised 1572** to include sub investigator, change of IRB address and addition of Dr. Herschfield's lab (for information only not a clinical lab) receipt acknowledgement 2/7
2/8/2002	FDA	Clinical/Tox	**Letter from FDA - Glen D. Jones**: received our IND and have the following comments and requests for information regarding our pre-clinical toxicology program
2/8/2002	BTG	Clinical/Tox	**Fax to Dr. Lauren Black:** Request for a teleconference to discuss proposed preclinical program; background material attached includes description of proposed preclinical program and summary of planned clinical program.

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Date	From	Info Type	Description
2/8/2002	BTG	Clinical/Tox	**S-006: Response to Request for Information** - Submissionof preclinical background information requested in preparation for upcoming teleconference to discuss the proposed preclinical program for Puricase. This information was previously faxed to Lauren B
2/11/2002	FDA	Correspondence	**Telephone Call Report:** from Lauren Black to schedule a telephone conference
2/11/2002	BTG	Correspondence	E-Mail to Dr. Black confirming if she received our fax on 2/7
2/12/2002	FDA	Correspondence	**Telephone Call Report**: w/Lauren Black and Marcy Califre: schedule teleconference to discuss proposed preclinical reproduction studies with FDA preclinical reviewer.
2/12/2002	FDA	Pharmacology/ Toxicology	**E-Mail**: Reply via e-mail from Dr. Black confirming conference call for Thursday 2/14 @ 9:00 am
2/12/2002	BTG	Pharmacology/ Toxicology	**E-mail to Dr. Black:** Change in date for teleconference call instead of Friday, have it Thursday, 2/14/01?
2/12/2002	BTG	Meeting Minutes	**E-mail to Dr. Black:** Minutes from FDA-BTG Pre-IND Meeting/Teleconference held on 11/13/00
2/12/2002	FDA	Correspondence	**E-mail from FDA:** Dr. Black confirming receipt of 15 page fax sent to her
2/13/2002	BTG	Correspondence	**E-Mail to Dr. Black**: Confirming conference call and list of attendees from BTG Corp. and BTG (Israel)
2/14/2002	BTG	Pharmacology/ Toxicology	**Telephone Call Report**: w/Lauren Black (FDA), Norman Barton, Marcy Califre, Arjen DeVos, Rami Nimrod, Rivka Zaibel on 2/14/02. **Subject**: Discuss Proposed Preclinical Program for Puricase™ with FDA Preclinical Reviewer. 9AM.
2/14/2002	FDA	Pharmacology/ Toxicology	**Telephone Call Report** from Dr. Lauren Black: Carcinogenicity Study: FDA Telephone Call. As a follow-up to the teleconference call held today 2/14 @ 9:00 am, Dr. Black responded to BTG's question regarding the requirement of the carcinogenicity study for
3/19/2002	BTG	Clinical/Tox	**S-007 Response to FDA Request for Information:** (acknowledgement receipt 3/20/02), Response to questions posed in 2/8/02 FDA letter provided; revised IB, IC and revised C0401 protocol (amendment # 2) were submitted along with responses and commitments to
3/26/2002	BTG	CMC	**S-008**: **Response to FDA for Information**: Response to FDA letter dated 1/18/02 regarding chemistry, manufacturing & controls development plans. (acknowledgement received 03/27/02)
4/2/2002	BTG	Pharmacology/ Toxicology	**S-009**: **Information Amendment**: As a follow up of the commitment noted in S#007 for submission of additional histopath information from dog study, amendment 1 to the final study report, #20-2-0189-00, entitled 'Repeated Dose Toxicity of "Puricase" in the D
4/18/2002	BTG	IND Safety Reports	**S-010**: **IND Safety Report:** Gout attack with draining tophus; Initial Report: Patient # 001-007 MDD (Dr. Sundy's site)
4/23/2002	BTG	Correspondence	**E-mail to Dr. Siegel** re: Protocol C0401 Issue to Discuss – Conference Call 4/24/02?
4/24/2002	BTG	Pharmacology/ Toxicology	**Fax to Andrea Weir,** new toxicologist for PEG. 27 pages fax to AW re: Pharmacology and Toxicology section from the IND for her review.
4/24/2002	FDA	Pharmacology/ Toxicology	**Telephone Call Report** w/Andrea Weir, Toxicologist from FDA phoned to discuss 'Proposed IV Dosing'
4/24/2002	BTG	Correspondence	**E-mail to Dr. Siegel** re: Protocol C0401 Issue to Discuss – Conference Call confirmation date – May 6th
4/24/2002	FDA	Correspondence	**E-mail from Dr. Siegel** re: Protocol C0401 Issue to Discuss – Conference Call alternative date – May 6th
4/25/2002	BTG	Clinical	**S-011 General Correspondence**: Notification to FDA of suspension of dosing in C0401 study(acknowledgement receipt 4/26/02)
4/30/2002	BTG	Correspondence	**E-mail from Marcy to Dr. Siegel**: Confirmation of teleconference to discuss Puricase BB-IND 10122 – Current Issues

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Date	From	Info Type	Description
5/2/2002	BTG	Correspondence	**E-mail from Marcy to Dr. Siegel**: confirming conference call – confirmation of new time
5/2/2002	FDA	Correspondence	**E-mail from Dr. Siegel**: confirming conference call – change of time
5/3/2002	FDA	Correspondence	**E-mail from Dr. Siegel** – confirming telephone number and the name of the allergist
5/3/2002	BTG	Correspondence	**E-mail to Dr. Siegel** – confirming telephone number for MCI
5/3/2002	BTG	Clinical	**Telephone Call Report with Dr. Siegel** – May 6th conference call attendees
5/6/2002	BTG	Clinical	**Telephone Call Report** (conference call) w/J. Siegel/A. Weir/D. Green: Discuss the status of protocol C0401 and BTG plans for pursuing intravenous dosing with Puricase (participants: N. Barton, M. Califre, A. DeVos, T. Eckhardt; A. Nimrod (was disconnecte
5/6/2002	BTG	Correspondence	**E-mail to Dr. Siegel** – teleconference today – attendees
5/7/2002	BTG	Clinical	**S-012 General Correspondence**: Notification of termination of C0401 study. Acknowledgement receipt 5/8/02
5/13/2002	BTG	Correspondence	**General Correspondence** - Letter to Dr. Kathyrn C. Zoon and Theresa Toigo Response to FDA letter regarding the clinical trials data bank
5/13/2002	BTG	Correspondence	**S-013: General Correspondence**: response to FDA letter regarding the clinical trials data bank (our acknowledgement received 05/15/02)
6/5/2002	BTG	Correspondence	**FAX:** Fax to Dr. Weir, a copy of S 014.
6/5/2002	BTG	Correspondence	**S-014**: **Response to FDA Request for Information** - During the May 6 teleconference, it was suggested that we submit the draft protocol for our subchronic toxicity study via the intravenous route in dogs for FDA review and comments. A copy of this draft pr
6/7/2002	FDA	Clinical	**Telephone Call Report**: PEG-Uricase – Call from Dr. Siegel (FDA) w/BK – received an informal call from Dr Siegel to discuss the abandoned subcutaneous protocol
6/12/2002	BTG	Pharmacology/ Toxicology	**Telephone Call Report**- w/Dr. Siegel, Marcy Califre to discuss Draft Toxicology Protocol for Repeated Dose IV Dog Study.
6/12/2002	BTG	Clinical	**Telephone Call Report** w/Dr. Siegel, Marcy Califre and Arjen DeVos: Respond to Dr. Siegel's question regarding the termination of the C0401 protocol
6/18/2002	BTG	Pharmacology/ Toxicology	**E-mail** to Dr. Weir from MC re: Comments on Toxicology Protocol
6/19/2002	FDA	Pharmacology/ Toxicology	**E-mail** from Dr. Weir to MC re: Comments on Toxicology Protocol (response)
6/20/2002	FDA	Pharmacology/ Toxicology	**Telephone Call Report** w/Dr. Weir and BK re: Draft Toxicology Protocol for Repeated Dose IV Dog Study – Teleconference
6/20/2002	BTG	Pharmacology/ Toxicology	**E-mail** from BK to Dr. Weir re: Comments on Toxicology Protocol (3rd response)
6/21/2002	FDA	Pharmacology/ Toxicology	**Telephone Call Report** w/Dr. Siegel and BK re: Product Reviewer's comments
6/21/2002	BTG	Correspondence	**E-mail** to Dr. Weir re: Confirmation of telephone conference call for Monday 6/24/02 @ 10:00am
6/24/2002	BTG	Pharmacology/ Toxicology	**Telephone Call Report**: conference call held on 6/24 w/Dr. Weir, BK, Mcalifre and R. Nimrod to discuss the draft 12 week IV, Subchronic toxicity protocol in dogs that submitted to FDA on June 5, 2002.

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Date	From	Info Type	Description
6/24/2002	FDA	Correspondence	**E-mail** from Dr. Weir with recommendation for re: 'recovery + challenge" issues with David Green
6/24/2002	FDA	Pharmacology/ Toxicology	**E-mail** from Dr. Weir re: Comments on Toxicology Protocol – Conference Call Confirmation time
7/3/2002	BTG	Pharmacology/ Toxicology	**E-mail to Dr. Weir:** BK sent the revised protocol via telefax and enclosing a copy of the same protocol & cover fax in addition to faxing it, it's also being e-mailed
7/3/2002	BTG	Protocol Amendments	**FAX: Revised protocol**: 12-week Repeated Dose Intravenous Injection Toxicity Study with Puricase in dogs (20 pgs), which included FDA recommendations, was faxed to Dr. Weir
7/8/2002	BTG	Correspondence	**E-mail to Dr. Weir:** regarding question if BTG plans to submit an official copy of 12 week dog study protocol to the submission? BK's response is yes we plan to submit a signed hard copy of the protocol to the IND
7/8/2002	FDA	Correspondence	**E-mail from Dr. Weir:** Confirmation receipt of e-mail and fax of revised protocol (sent 07/03/02)
7/23/2002	BTG	Correspondence	**Fax to Dr. Siegel re**: Proposed Protocol for Skin Test would like to discuss further at his convenience
7/24/2002	BTG	Pharmacology/ Toxicology	**S-015**: **Final protocol**: (study identification: Covance 6432-106) for the study '12 week repeated dose intravenous injection toxicity study with Puricase' (our acknowledgement received 07/26/02)
7/31/2002	BTG	Clinical	**E-mail to Dr. Siegel:** Outline for Skin Testing; what is the status of 7/23 faxed of the outline skin testing?
8/1/2002	BTG	Clinical	**S-016: Response to FDA Request for Information:** Highlights of May 15, 2002 Expert Meeting discussing immunogenicity and adverse reactions in the C0401 subcutaneous study
8/16/2002	BTG	Correspondence	**E-mail** to Dr. Siegel: Schedule a conference call to discuss the skin test outline.
8/19/2002	FDA	Correspondence	**E-mail** from Dr. Siegel: Response to conference call which has been confirmed for 8/27 @ 2:00pm.
8/21/2002	BTG	Correspondence	**E-mail** to Dr. Siegel confirming per his request, the new time for the conference call to discuss the 'skin test outline'.
8/27/2002	BTG	Correspondence	**Telephone Report** w/Dr. Siegel, Dr. Esayan (consulting immunologist), Arjen and BK to discuss the skin test protocol outline
9/9/2002	BTG	Clinical	**S-017**: **Protocol Amendment: Change in Protocol** Submitted documentation of IRB approval of C0401 Amendment #2 and IRB approval of the revised informed consent form per FDA request. A copy of the approved informed consent form was also submitted. (Acknow
9/30/2002	BTG	Clinical	**S-018: Information Amendment: Clinical**-Submit revised FDA 1572 form for Dr. Sundy adding Rex McCallum as a sub investigator (acknowledgement receipt 10/02/02)
10/1/2002	BTG	New Protocol	**S-019**: Protocol Amendment: New Protocol. Submit draft C0402 Phase I IV study protocol for review and comments. Dr. John Sundy, PI. (Acknowledgement receipt 10/2/02)
10/22/2002	BTG	Correspondence	**E-mail to Dr. Seigel:** Review of draft protocol C0402 interested to hear the comments
10/28/2002	BTG		**Telephone Call Report:** w/Dr. Siegel to discuss Confirmation of Teleconference: Nov. 5th at 4:00 pm
10/28/2002	BTG		**E-mail to Dr. Siegel:** Confirming Conference Call
10/28/2002	FDA		**E-mail from Dr. Siegel:** Schedule conference Call
10/29/2002	BTG	Correspondence	**E-mail from Dr. Siegel** regarding new time for Conference Call
10/29/2002	BTG	Correspondence	**Serial #020: General Correspondence: Sponsor Change of Address** –letter sent to Dr. Jones with new address/phone and fax #
10/29/2002	BTG	Correspondence	**E-mail to Dr. Siegel** confirming new date and time of conference call

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11/7/2002	FDA	Correspondence	**E-mail from Andrea Weir:** regarding availability of the week of 11/18 to discuss the animal data.
11/7/2002	BTG	Correspondence	**E-mail to Andrea Weir:** regarding a telephone conf. Call to discuss I.V. dog study and need her input regarding the submission of the available data
11/14/2002	BTG	Clinical	**SN 021 - Information Amendment: Clinical** we are amending our IND to include a revised Investigator's Brochure; Version 3 dated November 8, 2002. The IB was revised to include pharmacokinetic and safety information from our C0401 Phase I, subcutaneous cli
11/14/2002	BTG	Correspondence	**E-mail to Andrea Weir:** regarding draft preclinical toxicity report
11/19/2002	BTG	Pharmacology/ Toxicology	**E-mail to Dr. Weir:** Confirmation of 11/20/02 conference call along a list of the attendees and attachments of what will be discussed, 1) protocol 2) introductory statement and a summary table delineating the study that is available at this time.
11/20/2002	BTG	Pharmacology/ Toxicology	**Telephone Call Report:** with Dr. Weir, Marcy Califre, Arjen DeVos, Rami Nimrod and Shoshi Katz re: Ascertain whether the types of data currently available from 12-week iv, subchronic toxicity dog study, will be sufficient for FDA to determine the advisabil
11/20/2002	BTG	Pharmacology/ Toxicology	**E-mail to Dr. Weir:** forwarded an updated version of the summary table sent to Dr. Weir on 11/19
11/26/2002	BTG	Pharmacology/ Toxicology	**SN 022 - Information Amendment: Pharmacology/Toxicology:** submitting a copy of the interim summary report for Covance protocol 6432-106. All available individual animal data as well as all available summary data are included in this submission. To facil
12/3/2002	BTG	Correspondence	**Telephone Report:** Spoke to B. Friedman to determine the mechanism for obtaining a user fee waiver for BLA due to orphan drug status.
12/10/2002	BTG	Correspondence	**Telephone Report:** Call to A. Weir to determine status of review of interim dog toxicity report submission.
12/10/2002	BTG	Correspondence	**E-mail was sent to Dr. Weir from MC regarding IV Dog Toxicity Interim Report.** Follow-up on the status of submission Serial #022.
12/11/2002	FDA	CMC	**E-mail from Dr. Weir regarding status of Serial #022.** Dr. Weir just received our submission and it has not been reviewed yet however she'll do her best to get to it in the next couple of weeks.
1/7/2003	FDA	CMC	**E-mail from Dr. Weir regarding status of Serial #022.** Dr. Weir responded by stating she did review the study and has a couple of points to discuss with branch chief. She will be discussing these issues with him on 1/08/03 and will
1/7/2003	BTG	CMC	**E-mail to Dr. Weir regarding status of Serial #022:** Dr. Weir needs to discuss a few point with her Branch Chief.
1/8/2003	FDA	CMC	**E-mail from Dr. Weir regarding her completion of her review for study serial #022.** The data in the toxicology study is adequate to support our proposed clinical trial. However, she has one question that needs to be answered: If antibodies are detected i
1/14/2003	BTG	CMC	**Serial #023: Information Amendment: Chemistry /Microbiology:** the following documents were submitted to the FDA:
1/14/2003	BTG	CMC	**Telephone Report w/Dr. Weir:** left a message for Dr. Weir in response to the question posed in her 1/8/03 e-mail.

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2/12/2003	BTG	New Protocol	**Serial #025: Protocol Amendment: New Protocol: New Investigator** submitted the final C0402 protocol as well as Amendment #1 (dated 2/04/03) to this protocol. Also included in this submission is a signed 1572 form from a C.V. for John Sundy, Principal Inves
2/12/2003	BTG	Annual Report	**Serial #024: Annual Report** covering periods: 12/15/01 – 12/15/02 (acknowledgement receipt 2/13/03)
3/4/2003	BTG	Clinical	**Serial #026: Response to Request for Information:** At this time in accordance with the request made in your letter dated 11/20/01, we are submitting documentation of IRB approval for this protocol and informed consent form. (Acknowledgement received 03/0
4/1/2003	BTG	Protocol Amendments	**Serial #027: Protocol Amendment:** submission of Amendment #2 to Protocol C0402 (acknowledgement received 04/02/03)
5/20/2003	BTG	Correspondence	**Telephone Call Report:** Dr. Siegel advising that the PEG IND will remain with the same FDA reviewers after the transfer from CBER to CDER
6/12/2003	BTG	Correspondence	**Serial #028: General Correspondence:** Change of medical monitor from Ted Kramer to Zeb Horowitz. (Acknowledgement received 06/16/03)
6/17/2003	BTG	Clinical	**Serial #029: Response to Request for Information:** Submission of IRB approval and ICF for Amendment # 2 per FDA 11/03/01 letter. (Acknowledgement received 06/23/03)
6/20/2003	BTG	Correspondence	**Serial # 030: General Correspondence:** Sponsor Change of Name to Savient Pharmaceuticals, Inc. (acknowledgement received 06/30/03)
8/4/2003	Savient	Protocol Amendments	**Serial #031: Protocol Amendment:** Amendment #3; Protocol C0402 (IRB Approval/ICF) (acknowledgement received 08/05/03)
8/18/2003	Savient	Clinical	**Serial #032: Final Clinical Study Report**, Protocol C0401 (acknowledgement received 08/19/03)
9/15/2003	SPI	Clinical	**Serial #033: list of adverse events** from C0402 for orphan drug application for Dr. Michael Hershfield (our acknowledgement received 09/17/03)
9/26/2003	FDA	Correspondence	**Telephone Call Report:** Andrea Weir phoned to inquire if the final report for beagle dogs had been forwarded
10/6/2003	SPI	Correspondence	**Telephone Call Report:** Inquiry regarding new FDA Office of Biotechnology Products/Division of Therapeutic Proteins
10/8/2003	FDA	Correspondence	**Telephone Call Report:** Advisory Committee Meeting for development of products for gout
10/13/2003	SPI	Correspondence	**Background Information** for Arthritis Drug Advisory Committee Meeting on November 13, 2003
10/14/2003	SPI	Pharmacology/ Toxicology	**Serial #034: Information Amendment:** Pharmacology/Toxicology – Submission of final study report for 6432-106, 12-Repeated Dose IV Injection Tox Study with Puricase in Dogs and supporting TK, complement, immunogenicity and Puricase activity study reports.
10/14/2003	FDA	CMC	**Telephone Call Report:** from Kathleen Reedy informing SPI that the Advisory Drug Committee Meeting is being postponed until the first of next year, 2004
10/20/2003	SPI	Clinical	**Serial #035: General Correspondence:** presentation for the Arthritis Drug Advisory Committee Meeting
12/2/2003	SPI	CMC	**Serial # 036: Information Amendment: Chemistry/Microbiology:** Submission of Certificate of Analysis for Puricase lot # 26890051 to be used in C0403 clinical study (our acknowledgement received 12/03/03)
1/21/2004	SPI	Pharmacology/ Toxicology	**Serial #037: Information Amendment: Pharm/Tox:** Draft Toxicology Protocol for 39 week dog study and supporting documents: Protocol C0402 Preliminary PK Data and minutes from FDA pre-IND Meeting 11-13-00

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1/26/2004	SPI	Clinical	**Telephone Report:** Registration of C0403 Phase 2 study with the Clinical Trials Data Bank
2/9/2004	FDA	Correspondence	**Email** - Puricase BB-IND 10122; Request for teleconference to discuss toxicology protocol submitted in Serial # 37 on Jan. 21, 2004
2/12/2004	SPI	Annual Report	**Serial #038 – Annual report** covering the time period of 12/16/2002 – 12/31/2003 (acknowledgement received 02/20/04)
2/18/2004	SPI	Protocol Amendments	**Serial #039: Protocol Amendment:** submission of Amendment to Protocol C0403 (acknowledgement received 02/13/04)
2/19/2004	SPI	Correspondence	**E-mail to Dr. Weir** Puricase BB-IND 10122; Feb 25, 2004 teleconference Agenda to discuss toxicology protocol submitted in Serial # 37 on Jan. 21, 2004
2/24/2004	SPI	Pharmacology/ Toxicology	**E-mail: Dr. Weir** Puricase BB-IND 10122; Feb 25, 2004 teleconference to discuss toxicology protocol submitted in Serial # 37 on Jan. 21, 2004
2/25/2004	SPI/ FDA	Pharmacology/ Toxicology	**Telephone Report:** Teleconference with Dr. Weir Puricase BB-IND 10122; Feb 25, 2004 Agenda to discuss toxicology protocol submitted in Serial # 37 on Jan. 21, 2004
2/25/2004	SPI	Correspondence	**Fax: Dr. Gibbes** Puricase BB-IND 10122; Feb 25, 2004 teleconference (Puricase Activity Method)
2/25/2004	SPI	Pharmacology/ Toxicology	**Serial #040: Information Amendment:** submission of Amendment Pharmacology / Toxicology (acknowledgement received 03/01/04)
4/16/2004	SPI	New Investigator	**Serial #041: Protocol / Information Amendment:** submission of Amendments New Investigators and Clinical (acknowledgement received 04/22/04)
4/30/2004	SPI	Correspondence	**Telephone Report:** June 2-3 Arthritis advisory Committee Meeting
5/10/2004	SPI	New Investigator	**Serial #042: Protocol / Information Amendment:** submission of Amendments New Investigators and Clinical (acknowledgement received 05/18/04)
5/18/2004	SPI	Correspondence	**Serial #043:** General Correspondence: presentation for the Arthritis Drug Advisory Committee Meeting (Acknowledgement received 06/01/04)
6/3/2004	SPI	New Investigator	**Serial #044: Protocol / Information Amendment:** submission of Amendments New Investigators and Clinical (acknowledgement received 06/08/04)
6/23/2004	SPI	IND Safety Reports	**Serial #045: IND Safety Report:** 15 –Day Alert Report for pt. 006-002 – hypersensitivity reaction.(acknowledgement received 07/01/04)
7/8/2004	SPI	IND Safety Reports	**Serial #045/046: IND Safety Report:** 15 –Day Alert Report for pt. 006-001—aggravated gout (acknowledgement received 07/14/04) Serial number correction on 07/15/04(Acknowledgement Received 07/21/04)
8/13/2004	SPI	IND Safety Reports	**Serial # 047: IND Safety Report:** General Correspondence.- Summary Serious Adverse Event and Safety Information from the study C0403 sent to IRBs submitted to FDA.(acknowledgement received 08/13/04)
9/7/2004	SPI	IND Safety Reports	**Serial #048: IND Safety Report Follow-up:** Follow-up information for pt. 006-001 submitted (acknowledgement received 09/13/04)
9/21/2004	SPI	New Investigator	**Serial #049: Protocol/Information Amendment:** submission of Dr. Furie, PI to CO403 Protocol
10/12/2004	SPI	IND Safety Reports	**Serial #050: IND Safety Report Follow-ups:** Administrative changes to Mfr. Reports C0403-0001 and C0403-0002 submitted. 10/12/04 (acknowledgement received 11/02/04)
10/15/2004	SPI	New Investigator	**Serial #051: Information Amendment/ Protocol Amendment:** Submit Amendment #1 to protocol C0403 with IRB approval from Becker's site. (Acknowledgement received on 10/21/04). 10/15/04
11/2/2004	SPI	IND Safety Reports	**Serial # 052: IND Safety Report:** Initial Report-15 Day Alert Report for Pt.# 002-001(Dr. Becker's site)- anemia. 11/2/04

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2/1/2005	SPI	Protocol Amendments	**Serial # 053: Protocol/Information Amendment:** Submission of amended 1572 forms for Dr. Krohn, Baraf, Barkhuizen, Becker, and Moreland to include new lab; submission of documentation for Mountain States Health Laboratory. (Our Acknowledgement Received 2/1
2/22/2005	SPI	Annual Report	**Serial # 054: Annual Report** Covering the period January 1, 2004-December 31, 2004. (Our Acknowledgement Received 3/4/05).
3/3/2005	SPI	Protocol Amendments	**Serial # 055: Protocol Amendment: New Investigator, Information Amendment :** Submission of revised FDA 1572 forms for C0402 PIs Sundy, Kavanaugh and Furie
4/13/2005	FDA	Correspondence	**Telephone Report:** Dr. James Reese, CSO from the FDA called and referenced the letter we sent on April 15, 2005 requesting to reserve a date for EOP2 meeting. He noted that he needed a formal letter with the discussion points and questions in order to sc
4/15/2005	SPI	Correspondence	**Serial # 057: General Corres.** Request to reserve a date for the End-of-Phase 2 meeting date in mid-July, before the review division's calendar gets filled for that month. (Our Acknowledgement Received on 4/26/05).
4/15/2005	SPI	Clinical	**Serial #056: Information Amendment:** Clinical-Submission of Clinical Study Report C0402 (Our Acknowledgement Received on 4/26/05).4/15/05
4/19/2005	SPI	Correspondence	**Telephone Report:** Dr. James Reese, CSO from the FDA called and referenced the letter we sent on April 15, 2005 requesting to reserve a date for EOP2 meeting. He noted that he needed a formal letter with the discussion points and questions in order to sc
4/21/2005	SPI	Correspondence	**Serial # 058: General Corres.** Request to reserve a date for the End-of-Phase 2 meeting date in mid-July, before the review division's calendar gets filled for that month. (Our Acknowledgement Received on April 29, 2005).
5/5/2005	FDA	Correspondence	**Fax:** From FDA re Grants EOP 2 Meeting on July 26, 2005. 5/5/05
5/26/2005	FDA	Clinical	**Telephone Report:** Called Dr. Hull to discuss the requirements of QT/QTc studies for biologics. Dr. Hull noted that CBER never required such a study. He noted that such a study will not be required for Puricase as this is a very large molecule. He reco
6/21/2005	SPI	Briefing Book	**Serial # 059: General Corres** Per the FDA's telefax received on May 5, 2005, we've amended the IND to submit **eleven** copies of the Information Package for the End of Phase 2 Meeting on July 26, 2005 to Dr. Glen Jones, Director, and **three** copies were sent to
6/27/2005	SPI	Correspondence	**Telephone Report:** Dr. James Reese (CSO) confirmed receipt of EOP 2 meeting information package. The division will try to send questions/comments prior to the EOP 2 meeting on July 26, 2005. 6/27/05
7/5/2005	SPI	Clinical	**Telephone Report:** Jeff Fritsch from the FDA made an Inquiry regarding a Compassionate Use Study for PEG. 7/5/05
7/26/2005	SPI	Briefing Book	**Meeting Slides:** Presented at the FDA Meeting on July 26, 2005 in Rockville, MD for the EOP2 Meeting. 7/26/05
7/26/2005	SPI	Briefing Book	**Fax:** Dr. James Reese, PhD forwarded his 2nd draft of questions/comments prior to the EOP 2 meeting on July 26, 2005. 7/26/05
8/5/2005	SPI	Clinical	**Fax:** To Dr. Jeffrey Siegel requesting for review and input of proposal for phase 3 study plan. Savient needs to make a decision between two options for design of the pivotal trials, and cannot proceed to elaborate the Protocols in the absence of a deci

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8/15/2005	FDA	Clinical	**Telephone Call Report:** During the August 15th telephone conference, Dr. Jeffrey Siegel made comments on the phase 3 clinical development: Pivotal Trial Design.
8/16/2005	FDA	Clinical	**Fax:** Dr. James Reese, PhD forwarded a copy of his Memorandum of the July 26, 2005 FDA Meeting. Discuss CMC, Nonclinical and clinical issues relative to Phase 3 dev. 8/16/05
10/12/2005	SPI	Correspondence	**Telephone Call Report:** To Pratibha Rana, CSO regarding the submission of the draft phase 3 protocol.
10/13/2005	SPI	New Protocol	**Serial # 060: Protocol Amend** - Reference is made to the End of Phase 2 Meeting of July 26, 2005 (FDA Minutes dated August 16, 2005), submission of two Phase 3 development scenarios dated August 5, 2005, and a teleconference with Dr. Jeffery Siegel on Aug
10/14/2005	FDA	Correspondence	**Email:** From Pratibha Rana in reference to forwarding the draft Phase 3 Protocol to Dr. Siegel. 10/14/05
10/18/2005	SPI	Correspondence	**Email:** From Marcy Califre to FDA-Rosemarie Neuner regarding change in contact information at Savient Pharmaceuticals, Inc. 10/18/05
10/18/2005	SPI	Correspondence	**Email:** From Marcy Califre to FDA-James Reese regarding change in contact information at Savient Pharmaceuticals, Inc. 10/18/05
10/18/2005	SPI	Correspondence	**Email:** From Marcy Califre to FDA-Andrea Weir regarding change in contact information at Savient Pharmaceuticals, Inc. 10/18/05
10/18/2005	SPI	Correspondence	**Email:** From Marcy Califre to FDA-Pratibha Rana regarding change in contact information at Savient Pharmaceuticals, Inc. 10/18/05
10/18/2005	SPI	Correspondence	**Email:** From Marcy Califre to FDA-Jeffrey Siegel regarding change in contact information at Savient Pharmaceuticals, Inc. 10/18/05
10/27/2005	SPI	Correspondence	**SN061 General Correspondence: Change in contact person.** New contact at Savient Pharmaceuticals, Inc. is Murad Husain. (Our acknowledgement received on 11/3/05)
11/3/2005	FDA	Correspondence	**Email: From FDA-Prathiba Rana to Murad Husain regarding the submission of the SPA.**
11/8/2005	SPI	Clinical	**SN062 General Correspondence-Rationale Document for Phase 3**Protocol Design. (Our Acknowledgement received on 11/17/05)
11/8/2005	SPI	Clinical	**Email:** From Murad Husain to FDA – Pratibha Rana Submission SN062: General Correspondence-Rationale Document for Phase 3 Protocol Design.
11/8/2005	SPI	Correspondence	**Email:** From Murad Husain to FDA - Pratibha Rana regarding the submission of the Rationale document. 11/08/05
11/29/2005	FDA	Clinical	**Email:** From FDA-Pratibha Rana to Murad Husain the response to the draft SPA. The agency has several recommendations to the protocol that they want us to consider incorporating into the final submission.
12/12/2005	SPI	Clinical	**SN063 Request for Special Protocol Assessment-Clinical**
12/13/2005	SPI	Clinical	**Email:** Pratibha Rana's email request to forward the SPA desk copy to FDA Division of Anesthesia, Analgesia, and Rheumatology Products, 10903 New Hampshire Avenue. Bldg 22 Room: 3163, Silver Spring, MD 20903-0002.

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12/13/2005	SPI	Correspondence	**Email:** Response from Murad Husain to FDA-Pratibha Rana regarding her request to forward Desk Copy of 12/12/05 Submission SN063- Request for special Protocol Assessment-Clinical to her new address in Silver Springs, MD. An electronic copy of the cover le
12/13/2005	FDA	Response to FDA Request for Information	**Email:** From Pratibha Rana to Murad Husain to acknowledge FedEx tracking of Desk Copy
12/13/2005	SPI	Correspondence	**Fax:** Cover Letter of Submission SN063-Request for Special Protocol Assessment from Murad Husain to Pratibha Rana. Fax included 9 pages.
12/13/2005	SPI	Correspondence	**Email:** From Murad Husain to FDA-Pratibha Rana informing her that we have sent out the SPA on 12/12/05 via overnight express mail which included a desk copy for her in the package.
12/19/2005	SPI	Clinical	**Email:** Murad Husain forwarded corrected pdf copy of C0405 Protocol and the Perez-Ruiz Literature-"Effect of Urate-Lowering Therapy on the Velocity of Size Reduction of Tophi in Chronic Gout" Vol. 47. No 4. August 15, 2002 pp. 356-360, to the FDA-Pratibha
1/25/2006	SPI	Correspondence	**Email:** From Murad Husain to the FDA-Pratibha Rana regarding SPA: Our Response
1/26/2006	SPI	Information Amendment - Pharmacology/ Toxicology	**Submission:** SN064 Information Amendment: Pharmacology/Toxicology SN064. Submission of draft audited reports for studies 7533-100, WIL 441007 and WIL 441008. (Our acknowledgement received on February 2, 2006).
1/27/2006	FDA	Correspondence	**Fax:** From the FDA-Pratibha Rana: FDA letter dated 1/27/06 re: Response to a Request for SPA.
1/31/2006	SPI	Correspondence	**Email:** Murad posed questions to P. Rana: proposal for a Type A meeting to discuss SPA for phase 3 protocol; is it necessary to submit any more phase 2 summary data in support of begininningp hase 3?
1/31/2006	SPI	Correspondence	**Submission:** SN065 General Correspondence: Request For A Type Meeting for SPA review of protocol C0405 (Our acknowledgement received on 2/8/06).
2/6/2006	FDA	Correspondence	**Email: From Pratibha Rana-FDA regarding two questions, 1. Receipt of the fax requesting the Type A Meeting, 2. submission of the updated safety information, including all SAE's along with the phase 3 studies.**
2/7/2006	SPI	Correspondence	**Email:** Murad posed question regarding the composition of placebo to be used in the P3 clinical studies.
2/10/2006	FDA	Correspondence	**Email:** P. Rana notified Murad that his question was forwarded to the Product reviewers.
2/14/2006	FDA	Briefing Book	**SN066 Type A Meeting: Information Package**: Submission of revised C0405 protocol based on FDA recommendations in FDA letter dated 1/27/06; submission of RadPharm Charter for C0405 and request for a SPA review meeting for the revised protocol (Our acknowle
2/14/2006	FDA	Correspondence	**Email: From Pratibha Rana-FDA regarding the submission of the Information Meeting Package.**
2/16/2006	SPI	Annual Report	**Serial #067: Annual Report covering periods**: 1/1/05 – 12/31/05. (Our acknowledgement received on 2/21/06).
2/22/2006	SPI	Briefing Book	**Email:** From Murad Husain to FDA - Pratibha Rana forwarding the PDF version of the briefing package as attachments.

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2/22/2006	SPI	Correspondence	**Serial #068: Information Amendment: Clinical** Submission of revised Investigator Brochure, version 5 dated February 15, 2006 (Our acknowledgement received on 3/2/06).
2/28/2006	SPI	Briefing Book	**Email:** From Murad Husain to FDA – Pratibha Rana, forwarding E-copy of the Briefing Package # 2.
2/28/2006	SPI	Briefing Book	**Email:** From Murad Husain to FDA – Pratibha Rana, forwarding E-copy of the Briefing Package # 1.
3/1/2006	SPI	Clinical	**SN069: Information Amendment: Clinical.** Draft version of the Investigator's Brochure, Version 5.0 dated Feb 9 was inadvertently included in SN068, rather than the final version. The final Investigator's Brochure, Version 5.0 dated February 15, 2006 is in
3/1/2006	FDA	Correspondence	**Email:** FDA-Pratibha Rana regarding CMC Question.
3/1/2006	SPI	Correspondence	**Email:** From Murad Husain to FDA – Pratibha Rana, committing to forward 2 CD's of the January 26, 2006 SN064 submission via Fedex to Sara Stradley at the FDA in Silver Spring, MD on 3/2/06.
3/1/2006	FDA	Correspondence	**Email:** FDA-Pratibha Rana regarding CMC Question.
3/13/2006	FDA	Correspondence	**Email:** From Pratibha Rana to Murad Husain re: Clearance of letter.
3/13/2006	SPI	CMC	**Email:** From Murad Husain to FDA-Pratibha Rana re: Proposed TC with Dr. Rappaport.
3/15/2006	SPI	Clinical	**Email:** From Murad Husain to Pratibha Rana regarding email information request for AUC and Cmax data for 8mg dose of PEG-uricase.
3/15/2006	SPI	Correspondence	**Email:** From Murad Husain to FDA-Pratibha Rana re: 54-day study in rats was done, in study number 20-4-0188-00. Final study report was submitted in original IND SN #000.
3/15/2006	FDA	Correspondence	**Email:** From FDA-Pratibha Rana to Murad Husain re: receipt of CD, and question regarding the toxicology study in rats.
3/16/2006	FDA	Clinical	**Fax:** FDA Response- from Pratibha Rana with Response to questions on the 2/14/06 Meeting Package.
3/17/2006	SPI	New Protocol	**SN070: Special Protocol Assessment: Revised Protocol C0405** sent to Robert Rappaport, MD, Director, copy to Robert Meyer, Director, along with Desk Copy to Pratibha Rana. (Our Acknowledgement received on 3/27/06).
3/17/2006	SPI	Correspondence	**Email:** From Murad Husain to FDA-Pratibha Rana, providing Dial-In number and passcode for teleconference at 2pm.
3/20/2006	FDA	Correspondence	**Email:** From FDA-Pratibha Rana to Murad Husain with the information requested by the Pharmacology Toxicology Team needed to conduct proper review of the application.
3/20/2006	SPI	Correspondence	**Email:** From Murad Husain to FDA-Pratibha Rana, that we did formally submit to the revised protocol to the document room.

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3/20/2006	SPI	Correspondence	**Email:** From Murad Husain to FDA-Pratibha Rana the PDF E-Copy of the 3/17/06 SN070 Cover Letter.
3/30/2006	SPI	Correspondence	**Email:** From Murad Husain to FDA-Pratibha Rana. PDF Copy of cover letter for EOP2 Meeting Package was sent.
3/30/2006	FDA	Correspondence	**Email:** From FDA-Pratibha Rana to Murad Husain requesting a PDF copy of the cover letter dated June 21, 2005 containing response to information request.
4/3/2006	SPI	Correspondence	**Email:** From Murad Husain to FDA-Pratibha Rana re: request status of several issues possibly related to review of SPA; inquiry regarding pharm/tox. data and notification of upcoming CMC amendment pending receipt of FDA CMC Advice letter
4/4/2006	FDA	CMC	**Email:** From FDA-Pratibha Rana re: "CMC Advice Letter".
4/5/2006	FDA	CMC	**Fax:** From the FDA-Pratibha Rana "CMC Advice Letter"dated 4/4/06
4/10/2006	FDA	CMC	**SN071: Information Amendment: Chemistry, Manufacturing and Control.:** Submission of process and facilities information in support of the manufacture of the phase 3 clinical material
4/12/2006	SPI	Pharmacology/ Toxicology	**SN072: Response to FDA Request for Information:** Pharmacology/Toxicology. (2 Volumes). Submission of methods validation study reports , TK study reports, and immunogenicity study reports conducted in support of study #7533-100; submission of dosing soluti
4/20/2006	SPI	CMC	**SN073: Information Amendment-Chemistry, Manufacturing and Contro.** The Certificate of Analysis for placebo (lot# 5682003102) to be used in the upcoming Phase 3 clinical trials under Protocols C0405 and C0406 beginning in early May of 2006. (Our acknowle
4/25/2006	FDA	Correspondence	**Email:** From Pratibha Rana to Murad Husain re: SPA Status of PEG-uricase.
4/25/2006	FDA	Correspondence	**Email:** From Murad Husain to Pratibha Rana re: SPA Status of PEG-uricase.
4/27/2006	SPI	CMC	**SN074: Information Amendment-Chemistry Manufacturing and Contrd.** The revised Certificate of Analysis for Puricase (lot # 5682003100) to be used in the upcoming Phase 3 clinical trials under Protocols C0405 beginning in early May of 2006. (Our acknowled
4/28/2006	FDA	Correspondence	**Email:** From FDA Pratibha Rana to Murad Husain re: Summary of SPA Letter due on May 4th.
4/28/2006	SPI	Correspondence	**Email:** From Murad Husain to FDA-Pratibha Rana re: Summary of SPA Letter due on May 4th.
5/3/2006	FDA	Clinical	**Fax:** From the FDA SPA Response Letter.
5/4/2006		New Protocol	**SN075**: Protocol Amendment: New Protocol & Protocol Amendment: New Investigator. Protocol's submitted: Protocol C0405 "Randomized, Multicenter, Double-Blind, Placebo-Controlled Efficacy and Safety Study of 8mg PEG-uricase in Two Dose Regimens in Hyper

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5/5/2006	FDA	New Protocol	**Email:** Foma forwarded to the FDA-Pratibha Rana a copy of the cover letter to the submission of the final protocols (C0405 and C0406) and new investigators, SN 75
5/5/2006	FDA	Clinical	**SN076: General Correspondence**: In reference to the submission of May 4, 2006 SN075, the description of responsibilities for Kendle International Inc., our contract research organization (CRO), was inadvertently omitted. Two attachments, one for Study C04
5/23/2006	SPI	Correspondence	**Email:** From Murad to Pratibha regarding a proposal to meet with the Agency on CMC Development for PEG-uricase.
5/26/2006	SPI	Correspondence	**Email:** Telephone call from Murad to the FDA - Pratibha Rana to follow-up regarding the proposal to meet with the Agency on CMC Development for PEG-uricase.
6/5/2006	SPI	Correspondence	**Email:** From FDA - Pratibha Rana to follow-up with Murad regarding the proposal to meet with the Agency on CMC Development for PEG-uricase.
6/6/2006	SPI	Pharmacology/ Toxicology	**SN077: Information Amendment: Pharmacology/Toxicology**. Final Study Reports for WIL-41007 and WIL-41008 submitted. (Our acknowledgement received on 6/15/06).
6/9/2006	FDA	Clinical	**Email:** From FDA Pratibha Rana. The Review Team agrees with the company that he could be enrolled in their Phase-3 PEG-uricase trial.
6/20/2006	SPI	New Investigator	**SN078: Protocol Amendment: New Investigator**. We are amending the IND to include additional study sites for Protocol's C0405 (sites) and C0406 (sites). (Our acknowledgement received on June 26, 2006).
7/12/2006	SPI	Correspondence	**Email:** From Murad Husain to FDA-Pratibha Rana regarding proposal to amend Protocol's C0405 and C0407
7/13/2006	SPI	Protocol Amendments	**SN079: General Correspondence: Proposal to Amend Protocols**. We are proposing to amend protocols C0405 and C0406 (SPA) to allow participation of patients with inter-flare intervals less than a week to participate in the PEG-uricase Phase 3 program. (Our a
7/19/2006	SPI	New Investigator	**SN080: Protocol Amendment: New Investigators** and Sites: C0405: K. Hackshaw, J. Lisse, J. Sundy; C0406: A. Dillon, G. Gottschlich, D. Lalter, K. Kolba, L. Moreland, K. Oelke, S. Wolfe. We are amending the IND to include additional study sites for Protoc
7/22/2006	SPI	Briefing Book	**Fax:** Dr. James Reese, PhD forwarded his 1st draft of questions/comments prior to the EOP 2 meeting on July 26, 2005. 7/22/05
7/24/2006	FDA	Correspondence	**Email:** From Pratibha Rana to Murad Husain to make a formal submission to obtain the FDA's advise on two more minor modifications in our clinical program.
7/25/2006	FDA	Correspondence	**Email:** From Murad to the FDA-Pratibha Rana regarding changes to the protocol and what Regulatory Procedure we should follow.

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8/1/2006	FDA	Correspondence	**Email:** From Murad Husain and the FDA Sara Stradley regarding protocol Amendments. Per Sara Stradley, the amendments will need to be reviewed before commenting.
8/7/2006	SPI	Protocol Amendments	**SN081: General Correspondence: Proposal to Amend Protocols**C0405 & C0406 by removing the previously specified Open Label Extension dose Regimen, which will be determined upon enrollment into that study.
8/10/2006	SPI	Protocol Amendments	**SN082: Protocol Amendment: New Investigator.** We are amending our IND to include additional study sites for Protocol's C0405 and C0406.
8/18/2006	SPI	CMC	**SN083:** General Correspondence: Request for Type B CMC-Specific Meeting to discuss Puricase® (polyethylene glycol [PEG]-uricase) chemistry, manufacturing and controls related developmental issues (Ref. E-mail message from Ms. Pratibha Rana, dated June 9,
8/18/2006	FDA	Correspondence	**Email:** From FDA-Sara Stradley-Response to Request for Type B CMC-Specific Meeting. The FDA is scheduling meetings for late December.
8/18/2006	SPI	Correspondence	**Email:** From Murad Husain to the FDA – Sara Stradley regarding Request for Type B CMC-Specific Meeting.
8/28/2006	SPI	Correspondence	**Email:** From Murad Husain to the FDA-Sara Stradley following up on request for a Type B CMC Meeting for PEG-uricase.
8/30/2006	SPI	Correspondence	**Email:** From Murad Husain to FDA-Sara Stradley in response to Murad's email on August 30, 2006. The pre-meeting briefing package will be submitted 4 weeks prior to the meeting date. Murad has requested if Sara receives the meeting date earlier than expe
8/30/2006	FDA	Correspondence	**Email:** From FDA-Sara Stradley in response to Murad's follow-up email request for a Type B CMC Meeting for PEG-uricase on August 28, 2006. Sara Stradley would like to know when she can expect meeting package along with the 10 desk copies.
9/1/2006	FDA	Correspondence	**Letter:** From the FDA confirming the date and location of the CMC-Specific Meeting Type B.
9/1/2006	FDA	Correspondence	**Email:** From FDA-Sara Stradley in response to Murad's email on August 30, 2006 request for the meeting date. Sara has informed Murad that she has scheduled the meeting date on November 21, 2006 from 2-3pm, which will be held at the NIH Campus. Sara has
9/20/2006	FDA	Clinical	**Letter:** FDA response to proposed revisions to C0405 and C0406 protocols. FDA agreed to a protocol revision allowing inclusion of patients that experience gout flares that are not resolved for at least 1 week prior to the first study drug treatment, if t
9/22/2006	SPI	New Investigator	**SN084:** Protocol Amendment: New Investigator. We are amending our IND to include the following additional study sites for Protocol's C0405 & C0406.
10/13/2006	SPI	Clinical	**SN085: General Correspondence – Briefing Package** for CMC/Type B on November 21, 2006

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10/19/2006	SPI	Clinical	**SN086: General Correspondence- Request for waiver for IRB** for study sites in Canada (C0405) and Mexico (C0406). Also request release from obligation to send copies of IRB approvals and approved I/C forms.
10/31/2006	SPI	New Investigator	**SN087: Protocol Amendment: New Investigator**. Addition of PIs to C0405 and C0406; and submit revised FDA 1572 forms--- C0405- Nussbaum (new), Klein, Lisse; C0406 – Gorevic (new), Gottschlich.
11/9/2006	SPI	New Investigator	**SN 088: Protocol Amendment: New Investigator**- Addition of 4 sites in Mexico to C0405 and 4 sites in Canada to C0406.
11/16/2006	SPI	New Protocol	**SN089: Protocol Amendment: New Protocol**/ Change in Protocol – Submission of C0407 protocol; submission of Amendment # 2 to C0405 and C0406.
11/20/2006	FDA	Correspondence	**E-mail:** From Pratibha Rana to Murad Husain concerning the Division's response to the questions from CMC meeting package for November 21, 2006 meeting (SN085).
11/30/2006	FDA	New Investigator	**SN 090: Protocol Amendment: New Investigator**—Addition of PIs to C0405 and C0406. Michet added to C0405; Yazici added to C0406.
12/1/2006	SPI	Meeting Minutes	**SN 091: General Correspondence**: Type B CMC Meeting Minutes Held on 11/21/06 (Savient authored minutes)
12/4/2006	SPI	Correspondence	**Email:** From Murad to Pratibha concerning Parinda Jani missing from meeting attendee list held 11/21/06.
12/13/2006	SPI	IND Safety Reports	**SN 092: IND Safety Report- Initial Report**: Mfr. # 06US000052; patient # 101-005. Report of hospitalization due to pancreatitis. Becker's site.
12/21/2006	FDA	Meeting Minutes	**Email containing FDA letter dated 12/21/06:** From Pratibha Rana to Murad Husain concerning the Type B CMC Meeting held 11/21/06 between SPI and the FDA. FDA Meeting Minutes are attached to the e mail.
12/22/2006	SPI	New Investigator	**SN 093: Protocol Amendment: New Investigator** / Information Amendment: Clinical: Submit Fiechtner to C0407 study; submit revised 1572 forms for Codding (405); Oelke (406); and Yazici (406).
1/2/2007	SPI	Correspondence	**Email:** Follow up from Murad Husain to Pratibha Rana concerning "Request for an IRB Waiver for Foreign Study Sites".
1/24/2007	SPI	New Investigator	**SN 094: Protocol Amendment: New Investigator** / Information Amendment to include 3 additional study sites for Protocol C0405 and three PI's who will be conducting the C0407 Protocol.
2/21/2007	SPI	Annual Report	**SN 095:** Annual Report covering the period 1/1/2006 – 12/31/2006.
2/22/2007	FDA	Clinical	**Letter:** From Bob Rappaport to Murad Husain confirming the IRB Waiver has been granted in response to the letter request dated 10/19/06 from SPI.
2/22/2007	SPI	New Investigator	**SN 096: Protocol Amendment: New Investigator**- Addition of four sites to the C0407 protocol (Dillon, Gonter, Gottschlich, Riordan)
2/23/2007	SPI	IND Safety Reports	**SN 097: IND Safety Report**- Follow-up Report: Mfr # 06US000052; patient # 101-005.
3/19/2007	SPI	New Investigator	**SN098: Protocol Amendment: New Investigator** / Information Amendment – Information Amendment to include documentation for eight Principal Investigators who will be conducting the C0407 Protocol. Addition of 8 sites to C0407 (Baraf, Bookbinder, Butler, Fun
3/21/2007	SPI	Protocol Amendments	**SN099: General Correspondence: Proposal to Amend Protocols**C0405 and C0406.SPI would like to request comments and concurrence with the proposed revisions fom the FDA.
3/22/2007	SPI	Clinical	**SN100: Information Amendment: Clinical**– SPI amended IND:10122 to include a revised Investigator's Brochure, v 6.0 dated 3/16/07.

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3/29/2007	SPI	CMC	**E mail**: From Murad Husain to Pratibha Rana--question regarding whether or not accelerated stability data will be required for the BLA submission.
4/2/2007	FDA	CMC	**E mail**: From Lisa Basham to Murad Husain—Has forwarded SPI inquiry to product reviewer. Asked Murad to check back next week if no response by then.
4/16/2007	FDA	CMC	**Email:** From Lisa Basham- response to Murad's follow-up email originally sent to Pratibha Rana dated March 29, 2007, concerning a question SPI had proposed to submit drug product stability data from both accelerated and real-time conditions in the BLA
4/20/2007	SPI	New Investigator	**SN # 101 – Protocol Amendment – New Investigator**- Add 2 PIs to C0407 (Fraser and Thurmond-Anderle)
5/9/2007	FDA	New Investigator	**SN # 102 – Protocol Amendment – New Investigator** –Add 6 PI's to CO407(Barkhuizen, Torres, Codding, Mandel, Huff, D'Ambrosio) and submit 1 revised 1572 form for C0405 (Yood).
5/17/2007	SPI	New Investigator	**SN # 103 – Protocol Amendment: New Investigator**- Add 9 PIs to C0407 (Becker, Hackshaw, Kerr, Lisse, Nussbaum, Oelke, Oza, Raja, Sundy) and submit 2 revised 1572 forms for C0406 (Dillon, Torres).
5/17/2007	SPI	Clinical	**Email:** from Foma Rashkovsky request for written concurrence from FDA regarding implementation of changes to the C0405 and C0406 protocols due to the current hydrocortisone shortage
5/22/2007	FDA	Clinical	**Email:** From Lisa Basham to Foma Rashkovsky: re: Phase 3 studies and shortage of hydrocortisone. SPI request not to substitute long-acting corticosteroid for hydrocortisone. FDA suggested submission to IND.
5/25/2007	FDA	Clinical	**Email:** FDA suggesting we submit a protocol change to the IND for their review and they will respond.
5/30/2007	SPI	Clinical	**SN 104: Information Amendment – Clinical** – Reports on Plasma Uric and Serum Uric Samples and use of a proposed correction factor in Protocol C0405 and C0406.
6/1/2007	SPI	Protocol Amendments	**SN 105: Change in Protocol** Amendment 3 for C0405 and C0406 Amendment provides guidance for using alternative corticosteroids when the hydrocortisone shortage necessitates a substitution.
6/14/2007	SPI	Protocol Amendments	**E-Mail:** Request from Murad Husain to Lisa Basham at FDA: 1. Status update of Amendment 3 to C0405 and C0406 SN 099 2. Request for Type B Meeting in July or August - re: Clarification on SAP submission to the BLA
6/18/2007	SPI	Clinical/CMC	**SN 106: Protocol Amendment: New Investigator:** Add New Investigators to C0407: Steven Klein, MD, Randal Earl White, MD, Robert A. Yood, MD. Revised 1572 for: Alan Kivitz, MD (C0406) add SI (Smith). **Information Amendment** Chemistry/Microbioology: New cont
6/20/2007	SPI	Clinical	**Telephone Contact Report**: Murad called Lisa Basham today, 6/20/07, as a follow-up to our e-mail message from June 14 proposing for a Type B meeting to present and agree on clinical data format for our upcoming BLA, and to enquire about the status of our p
6/20/2007	SPI	Protocol Amendments	**SN 107: Protocol Amendment** – Change in Protocol: C0407 Amendment 1 - This amendment contains the provisions of draft Amendment # 3 to C0405/6, submitted as SN099. Amendment provides for increased enrollment time window between 405/6 and 407; requirement f
7/6/2007	SPI	Clinical	**SN 108: Protocol Amendment – Change in Protocol** C0407 Amendment 1 - This amendment contains the provisions of draft Amendment # 3 to C0405/6, submitted as SN099. Amendment provides for increased enrollment time window between 405/6 and 407; requirement f
7/12/2007	SPI	Clinical	**SN 109: Protocol Amendment – Change in Protocol**: Amendment 4 to C0405 and C0406 which includes revisions submitted as Amendment #3 in SN 105 on June 1, 2007.

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7/19/2007	SPI	Clinical	**SN 110: Information Amendment and General Correspondence** – Submitted SAP for review and concurrence for C0405, Request for Type C Meeting to reach agreement on proposed SAP and specific clinical data in the BLA, and questions.
7/23/2007	SPI	Clinical/CMC	**SN 111 – Information Amendment: Chemistry/Microbiology and Clinical – Protocol Amendment: New Investigator:** New PI for C0407 Janet Pope, MD, Revised FDA 1572 A. Kavanaugh, MD to include additional subinvestigator, Hennigan, COA for Lot 7088, COA for lot
8/1/2007	SPI	Protocol Amendments	**E-mail** from Murad Husain to Lisa Basham on August 1, 2007 and August 2, 2007 for follow-up on SN 104, Info Amendment: Clinical; SN 105 – Protocol Amend – Change in Protocol – Amend #3 ; SN 109 Protocol Amend – Change in Protocol – Amend #4 to Phase III; S
8/2/2007	FDA	Protocol Amendments	**E-mail** from Lisa Basham: Meeting request was denied by FDA will respond in writing; FDA is waiting for a response from their Stat Team leader on projected timeframe on the SAP and will notify us as soon as they have the information.
8/3/2007	SPI	Clinical	**SN 112 – Information Amendment – Clinical**: Amended IND to include six bioanalytical assay validation. In addition to FDA recommended antibody assays, we have validated an "Enzyme Linked Immunosorbent Assay (ELISA) for the Detection of Anti-Uricase IgG an
8/17/2007	SPI	New Investigator	**SN 113 – Protocol Amendment: New Investigator:** Added Daryl K. MacCarter, MD, PI, to C0407. Amended Andre Barkhuizen, MD, PI, to 0406 for change of address
9/13/2007	FDA	Protocol Amendments	**E-Mail** from Lisa Basham dated 9/13/07 re: follow- up on 4 submission: SN 104, Info Amendment: Clinical; SN 105 – Protocol Amend – Change in Protocol – Amend #3 ; SN 109 Protocol Amend – Change in Protocol – Amend #4 to Phase III; SN 110 Info Amend – Clini
10/1/2007	FDA	Protocol Amendments	**Email** from Lisa Basham dated 8/2/07 status of 4 submissions: Items 1-3 is circulating; waiting for final response to Item 1 and the pkg (item 4) but expect to have them within the next week or so. Send meeting request for CMC meeting.
10/1/2007	SPI	Protocol Amendments	**Email** to Lisa Basham dated 10/1/07on status of 4 submissions: SN 104, Info Amendment: Clinical; SN 105 – Protocol Amend – Change in Protocol – Amend #3 ; SN 109 Protocol Amend – Change in Protocol – Amend #4 to Phase III; SN 110 Info Amend – Clinical Sta
10/2/2007	SPI	Correspondence	**SN 115 - General Correspondence - Request for Review of a Proposed Proprietary Name**: Submitted Tophuric and Puricase®. Included Summary of Draft Labeling, Rationale for Choice of Proposed Proprietary Name(s), Executive Summary of Development Program, USA
10/2/2007	SPI	New Investigator	**SN 114 – Protocol Amendment – New Investigators**: Submitted to C0407: John L. Harshbarger, MD, Brian F. Mandell, MD, PhD, Craig Scoville, MD, PhD, Edward T. Treadwell, MD
10/3/2007	SPI	Correspondence	**Email from Murad to Lisa Basham** requesting amount of time before a decision is made on the proposed name(s).
10/3/2007	FDA	Correspondence	**Email from Lisa Basham on October 3, 2007** informing SPI it takes approx 180 days, plus a week or so, for a determination of the proposed name.
10/4/2007	FDA	Change in Protocol	**Email** with FDA Advice Letter on SN 105 and 109 RE: C0405 and C0406 Protocol Changes
10/4/2007	FDA	Clinical	**FDA letter**- regarding response to SN 105 and 109 containing protocol amendments for C0405 and C0406
10/8/2007	SPI	Change in Protocol	**SN 116 – GC** – Response to FDA's letter of 10-4-07 regarding C0405 and C0406 protocol amendments 3 and 4 submitted as SN105 and 109 on June 1 and July 12, 2007, respectively
10/11/2007	FDA	Correspondence	**FDA Letter dated 10/4/07** hard copy - regarding Amendments Submitted June 1 and July 12, 2007 for C0405 and C0406

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10/11/2007	FDA	Correspondence	**E-mail from Lisa Basham** advising Murad Husain of contact person to establish email encryption between FDA and SPI.
10/11/2007	SPI	New Investigator	**SN 117** – New Investigators for C0407 – Mexico: Ruben Burgos-Vargas, MD Sergio Ramon Gutierrez-Urena, MD Nora Janitzia Vazquez-Mellado Cervantes
10/12/2007	SPI	Pharmacology/ Toxicology	**SN 118:** Final Study # 7533-100 - 39-Week Repeated Intravenous Injection Chronic Toxicity and Toxicokinetic Study with Puricase® in Dogs with a 12-week recovery
10/12/2007	SPI	Correspondence	**Email:** Ken Royer, from IT, contacted Wendy Lee at FDA for assistance and details involved with email encryption set up between FDA and SPI.
10/15/2007	FDA	Clinical	**Email** with requested document attached; sent in response to FDA email request dated 10/15/07 for a copy of SN 104 containing analytical method being used in assaying plasma uric acid in Phase 3
10/19/2007	FDA	Correspondence	**Email** from FDA to Ken Royer re: Encryption Process with attachment of detailed software/equipment for encryption set-up between FDA and SPI
10/24/2007	FDA	Correspondence	**Email** from FDA's Wendy Lee to Ken Royer, IT, follow-up on encryption procedure between Savient and FDA
11/6/2007	FDA	Clinical	**Email** from Lisa Basham re: FDA has accepted Savient proposals in SAP submitted in SN110,there is one outstanding question regarding CDISC STDM
11/7/2007	SPI	Protocol Amendments	**SN 119 – Protocol Amendment** – New Investigators: C0407 Clement Michet; revised FDA 1572 forms for C0406 Kurt Oelke and Arnaldo Torres; C0405 John Huff, Clement Michet, Jr., Michael Yood, MD
11/16/2007	FDA	Clinical	**Email** from Lisa Basham re: response to request for update regarding pending issues: Uric Acid Test Method and SAP. May know by next week, 11/19-23/07
11/21/2007	SPI	CMC	**SN 120** – CMC update: Update to the manufacturing information for mPEG-NPC; and notification of a change in the contract filler
11/30/2007	SPI	Protocol Amendments	**SN 121** – Protocol Amendment – New Investigator for C0407 – Mexico - Hilario Ávila Armengol, MD
12/5/2007	FDA	Correspondence	**Email** – FDA's response to when a Type B meeting can be scheduled – April 2008 is the earliest.
12/12/2007	FDA	Correspondence	**Email** – Request to Lisa Basham for Fax Number to send Dr; Rappaport Confidential Information
12/13/2007	SPI	Clinical	**SN 122** – Preview of Phase 3 top line efficacy and safety results prior to issuance of press release
12/14/2007	SPI	CMC	**SN 123** – Request for Type B Pre-BLA Meeting to discuss content and format of the BLA
1/10/2008	FDA	Correspondence	**Email** from L. Basham-Pre-BLA Meeting is scheduled for April 17, 2008
1/10/2008	SPI	Protocol Amendments	**SN 124** – Submitted Amendment 2 to C0407 and 4 revised 1572;s: 2 for C0405 Michet and Sundy, and 2 for C0407 Barkhuizen and Lisse
1/29/2008	FDA	Clinical	**FDA** letter dated 1/29/08 attached to 1-30-08 L. Basham e mail: FDA response to SN110- 7/19/07 Request for Type C Mtg to discuss SAP
1/30/2008	FDA	Clinical	**Email** from Lisa Basham with attached FDA Letter in response to SN110 dated 7/19/07 Request for Type C Mtg to discuss SAP
1/31/2008	FDA	Correspondence	**Email** from L. Basham requesting our dialogue with CMC Reviewers, at NIH Campus to go through Lisa Basham.

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Date	From	Info Type	Description
2/22/2008	SPI	Annual Report	**SN 126** – 2007 Annual Report
2/22/2008	SPI	Protocol Amendments	**SN 125** – Submitted Protocol C0409 and Revised 1572 for Norman Gaylis
3/13/2008	SPI	Briefing Book	**Email** from L. Basham on status, copies, and delivery of Briefing Book.
3/17/2008	SPI	Briefing Book	**SN 127** – Briefing book outlining questions for April 17, 2008 FDa Meeting
3/17/2008	SPI	Correspondence	**Email to FDA** testing Encrypted Message capability
3/20/2008	SPI	Briefing Book	**Email** from L. Basham requesting 14 additional copies of pre-BLA meeting BB and from M. Husain inquiring if BB is adequate background for the meeting
4/3/2008	SPI	Protocol Amendments - New Investigator	**SN 128** – New Investigators for C0409 Drs. Baraf and Barkhuizen. Revised 1572 for Barry Getzoff for C0407
4/3/2008	SPI	Briefing Book	**Email** response from FDA regarding setting up encrypted messaging to enable safe e-transmission of supportive clinical pharmacology data for pre-BLA meeting package
4/4/2008	SPI	Other - Addendum to Briefing Book	**SN 129 – GC** – Addendum to Pre-BLA Meeting Package submitted on 3/17/08 per FDA request: Clinical Pharmacology Data Sets
4/7/2008	SPI	Briefing Book	**Email** to Lisa Basham with PDF SN 129 attached Addendum to Briefing Package with Clinical Pharmacology data.
4/10/2008	SPI	Briefing Book	**Email** to L. Basham follow-up to request for Agency answers to Pre-BLA questions and request to include an additional CMC question.
4/15/2008	FDA	Briefing Book	**FDA letter** dated 4/15/08 -Attached to 4/15/08 Email from L. Basham RE: Agency responses to 4/17/08 Pre-BLA Meeting Questions
4/15/2008	FDA	Briefing Book	**Email** from L. Basham with attached 4/15/08 FDA Letter containing Responses to Pre-BLA Meeting Questions
4/22/2008	FDA	Correspondence	**Email** from L. Basham responding to Savient email requesting a status update on the FDA review of proposed proprietary name- still checking
4/25/2008	FDA	Correspondence	**Email** from L. Basham correcting Attendee List for Pre-BLA Meeting to reflect actual attendees
4/25/2008	FDA	Correspondence	**Email** from L. Basham confirming CMC Questions to be discussed at the scheduled pre-BLA meeting and confirming final Savient Attendee List
4/30/2008	FDA	Correspondence	**Email** from L. Basham with informal FDA response to Savient proprietary name request – Tophuric deemed acceptable
4/30/2008	SPI	Information Amendment - Clinical	**SN 130** Submit revised 1572 forms for C0407 Investigators; Dillon, Fiechtner, Gottschlich, Oza, Raja, Yood and submit RadPham Charters to be used with C0407 and C0409
5/12/2008	SPI	General Correspondence - Meeting Minutes	**SN 131** – Savient Minutes from 4-17-08 Pre-BLA Meeting
5/13/2008	FDA	Correspondence	**FDA Letter** – FDA Response (No Objection at this time) to Savient Request for Review of proposed proprietary name -Tophuric
5/14/2008	FDA	Correspondence	**Email** from L. Basham assigning Submission Tracking Number 125293/0/0 for the BLA
5/19/2008	FDA	Meeting Minutes	**Email** from L. Basham with attached FDA version of 4-17-08 Pre-BLA Meeting Minutes. FDA letter dated 5-16-08.

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5/22/2008	SPI	General Correspondence - Meeting Minutes	SN 132 – General Correspondence - Savient Pharmaceuticals, Inc.comments on FDA version of 4-17-08 Pre-BLA Meeting Minutes
6/9/2008	SPI	Protocol Amendment - New Investigator	SN 133 - Protocol Amendment - New Investigator - Added John Sundy to PI for C0409
6/12/2008	FDA	Meeting Minutes Comments	**Email** Request from Murad for comments on meeting minutes sent in SN 132. Lisa heard nothing from the chemists on item 3. Unofficially, the clinical team gave okay for revision 1 and 2
7/9/2008	FDA	Email	**Email** from L. Basham confirming CMC and Clinical points of Meeting Minutes are acceptable. Submission date moved to Mid-October due to Alternate Mfg Site
7/9/2008	SPI	Protocol Amendment and Information Amendment	SN 134 – Protocol Amendment – New Investigator for C0409 Saima Chohan, MD, with CV, IRB Approval and and Informed Consent Form. Revised 1572 for C0407 for Dillon, Huff, and Oza, Information Amendment - Investigator's Brochure, Version 7.0
8/12/2008	FDA	Email	**Email** from L. Basham to send Safety updates on day 120. Minutes have not been issued yet.
8/27/2008	SPI	Information Amendment - Clinical	SN 135 - Information Amendment - Revised RadPharm Independent Review Charter Version 3
8/27/2008	FDA	Email	**Email** from L. Basham - Trying again to get feedback on the comparability protocol. Will try to get minutes this week
9/4/2008	FDA	Email	**Email** from L. Bahsam - Response to alternate manufacturing site
9/10/2008	FDA	Email	**Email** from L. Basham - Discrepancy in what happens when patients discontinue use of drug
9/22/2008	SPI	Submission	SN 136 - Protocol and Information Amendment - Clinical - Add new PI to take over for Daryl MacCarter(Collins) and change site address.
9/22/2008	FDA	Email	**9-22-08 - Email** from L. Basham with Pre-BLA Meeting Minutes Final Attached
9/29/2008	FDA	Email	**9/29/08 FDA Email** - What is your ETA for PEG BLA - End of October
10/6/2008	FDA	Email	**Email** from L. Basham - re: Cardiovascular Events. Request to submit an accounting and safety analysis of all deaths reported with the product along with a safety assessment of all serious cardiovascular thromboembolic adverse events. Include all serious
10/7/2008	SPI	Email	**Email** from M. Husain re: CV Events. Response to FDA Request for information re: CV Events
10/15/2008	FDA	Email	**Email** from L. Basham re: Review of Proprietary Name w/BLA and CV Events Teleconference
10/15/2008	FDA	Email	**Email** from L. Basham re: PPI, REMS, submission of Proprietary Name, DP and DS Info
10/24/2008	FDA	Email	**Email** from L. Basham re 3 Questions - Data submitted to FDA no later than 3 months into review period.
11/4/2008	SPI	Information Amendment - Clinical	SN 137 - Submitted revised 1572s for Butler, Gaylis, Lisse, Mandel and Yood for C0407
1/19/2009	SPI	Information Amendment - Clinical	SN 138 - Submitted revised 1572's for Drs. Baraf, Gottschlich, Leonard(replaced Riordan), Wolfe for C0407
1/28/2009	SPI	Safety Report	SN 139 - Submitted Initial Report for Patient # C0406/325-001 from C0407-AE: Necrotizing Skin Lesions on Face and Hands (Dermatitis). Mfr Report # 09US000316.

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Date	From	Info Type	Description
2/12/2009	SPI	Safety Report	**SN 140** - Submitted Follow-up report for Patient # C0406/325-001 from C0407- AE: Necrotizing Skin Lesions on Face and Hands (Dermatitis). Mfr Report # 09US000316.
2/23/2009	SPI	Annual Report	**SN 141** - Annual Report covering period 1/1/08 to 12/31/08
2/27/2009	SPI	Info Amend - Clinical	**SN 142** - Revised 1572 for Protocol C0407 for Baraf, Lisse, Nussbaum, Scoville and C0409 Baraf
3/20/2009	SPI	Safety Report	**SN 143** - Submitted Follow-up Report for Patient #C0406/325-001 from C0407 - AE: Necrotizing Skin Lesions on Face and Hands
3/27/2009	SPI	Info Amend - Clinical	**SN 144** - Submitted Amendment 3 to C0407 protocol extending treatment duration beyond 24 months
6/3/2009	SPI	Info Amend - Clinical	**SN 145** - Submitted Revised 1572's for 22 C0407 PI's added 2 new laboratories: Synarc SAS in Lyon, France; and Charles River Labs Preclinical Services Montreal Inc. in Senneville, Quebec, Canada. Three revised DA 1572's include revisions to the Study Site
7/2/2009	SPI	Info Amend - Clinical	**SN 146** - Submitted 2 additional labs to be used in the C0407 Study on Revised 1572's and updated addition and deletion of Subinvestigators: Becker, D'Ambrosio, Fraser, Fung, Getzoff, Hackshaw, Harshbarger, Huff, Kerr, Lisse, Mandel, Michet, Raja, Sundy, T
10/28/2009	SPI	Protocol Amendments	**SN 147 - Protocol Amendment: Investigators' Data:** Submitted 30 updated 1572s for Study C0407 (Baraf, Barkhuizen, Becker, Bookbinder, Butler, Collins, A'Ambrosio, Dillon, Fung, Fung, Gaylis Getzoff, Gonter, Gottschlich, Hackshaw, Harsbarger, Hill, Holt, Hu
12/16/2009	SPI	Protocol Amendments	**SN 148 - Protocol Amendment: Investigators' Data:** Submitted 6 updated 1572s for Study c0407 (Barkhuizen, Fraser, Scoville, Sundy, torres, White) addition of Princeton RadPharm lab.
3/17/2010	SPI	Annual Report	**SN149 Annual Report** - reporting period 1/1/09-12/31/09
3/29/2010	SPI	Info Amend - Pharmacology/ Toxicology	**SN 150 Information Amendment: Phamacology/Toxicology:** submitted final reports for WIL 441015, 441016 and 441017.

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10/6/2006	FDA	Administrative	FDA's Official Minutes of Type A Meeting held on September 14, 2009. Purpose of mtg was to discuss deficiences contained in CRL dtd 7/31/09.
10/12/2006	SPI	Administrative	Letter - Disposition of Drug Product Batches, ltr confirming FDA request that peg drug product batches for post-approval commercial purpose using Process B are rejected
10/31/2008	SPI	Administrative	Informing L. Basham BLA has been submitted and attaching a copy of the receipt for transmission
10/31/2008	SPI	Administrative	Letter to Office of Regional Operations in Rockville, MD certifying Savient's Electronic Signature on all correspondence as legally binding
10/31/2008	SPI	Administrative	Letter notifying NJ District Office that BLA was submitted 10/31/08
10/31/2008	SPI	Proprietary Name	**Submission 0000** - Initial Biologic Licenisng Application (BLA) Submission for TRADNAME (pegloticase)...
11/3/2008	FDA	Administrative	L. Basham informing Savient that Diana Walker is the new PM for BLA 125293.
11/5/2008	SPI	PAI	Email to Mary Farbman regarding FDA request to perform PAI at BTG in January and not March and informing FDAthat BTG could be schedule a pegloticase batch process for weeks of January 18 or 25th.
11/5/2008	FDA	PAI	Email from M. Farbman thanking M. Husain for info
11/5/2008	SPI	PAI	Email from M. Husain informing M. Farbman that it takes a month of manufacture a batch of pegloticase and asking for the FDA dates so we can arrange for this batch to be made.
11/5/2008	FDA	PAI	Mary E. Farbman responding to Savient's 11/5/08 email regarding PAI at BTG informing us they will let us know the date of inspection for BTG
11/10/2008	FDA	Proprietary Name	Diana L. Walker, new FDA PM, requesting a tradename review submission and submitting as a separate submission to BLA. Also requesting Savient to include everything submitted in prior tradename submissions etc...
11/10/2008	SPI	Proprietary Name	Email from M. Husain responding to 11-10-08 email from FDA regarding tradename review.
11/10/2008	FDA	Proprietary Name	Response to tradename review request acknowledging request and asking about the timeline of this review...
11/12/2008	FDA	Acknowledgement	FDA letter acknowledging receipt of BLA Submission 0000
11/13/2008	FDA	Acknowledgement	Diane Walker/FDA sending copy of acknowledgement letter for BLA - Submission 0000
11/14/2008	SPI	Proprietary Name	**Submission 0001** - proposing KRYSTEXXA as proprietary name for pegloticase. Re: is made to FDA's 5/13/08 ltr indicating no objections to Tophuric as proprietary name, and Savient now informing that Tophuric is second preference.
11/17/2008	SPI	PAI	Providing information for dial in numbers for 1:30 p.m. TC and attaching formal letter to email describing mfg. schedule to best accommodate FDA plan for PAI
11/18/2008	SPI	PAI	Mary Farbman/FDA re: PAI - providing revised mfg. schedule at BTG based on 11/17 discussion, including hotel accommodation info provided by BTG.
11/19/2008	SPI	PAI	FDA email sending revised scheduled re PAI at BTG in February...
11/20/2008	FDA	ACC	Nicole Vesely introducing herself and advising Savient of upcoming publication of AAC Meeting with a "Letter to Sponsor" attached
11/20/2008	FDA	ACC	Nicole Vesely, PharmD, Designated Federal Official, AAC, advising Savient of tentatively scheduled 3/5/09 AAC mtg., documents needed and providing format requirements of documentation, etc.

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11/21/2008	FDA	ACC	Diane Walker informed Savient our drug classification is new molecular entity (NME) and addressed type of general presentation that was required at AAC mtg…
11/21/2008	SPI	Info Request/CMC	Sent FDA proposal with revised mfg. schedule and requesting M. Farbman's address.
11/21/2008	SPI	Info Request/CMC	Brief summary of 11/17/08 Teleconference regarding revised Manufacturing schedule for proprosed PAI at BTG in Israel
12/1/2008	FDA	Info Request/CMC	Email dated 12/1/08 confirming FDA PAI at BTG 1/28/08 to 2/5/08
12/4/2008	FDA	Administrative	FDA requesting number of attendees at AAC meeting
12/5/2008	SPI	Proprietary Name	**Submission-0002** Amendment to Proprietary Name Review requesting we replace proprietary name, requesting to replace previously submitted and acccepted second choice name Tphuric with Exercase.
12/9/2008	SPI	Amendment/CMC	**Submission 0003** - Letter to FDA Confirmation of Mfg Schedule for PAI with BTG in 2009
12/10/2008	FDA	Acknowledgement	Diana Walker of FDA acknowledging receipt of Submissions 0002 and 0003
12/11/2008	SPI	ACC	Sent FDA List of Consultants for AAC Mtg tentatively scheduled for 3/5/09
12/16/2008	FDA	Info Request/Clinical	FDA requesting Savient submit by 12/22/08 1. assay validation reports for all immunogenicity assays; 2. SOPs for each immunogenicity assay; and 3. relevant supporting assay development data used to establish routine operation parameters of the assay but
12/16/2008	FDA	PAI	FDA requesting PAI Documents to be on site and requesting hotel reservation information for upcoming PAI in 2009.
12/16/2008	FDA	PAI	Document list attached to FDA12/16/08 email requesting that these docs are available for PAI.
12/18/2008	FDA	Info Request/Clinical	S Leibenhaut of FDA Office of Compliance with three questions regarding PUA Data/Timepoints. (See email response to queries on 12/22/08)
12/18/2008	FDA	Info Request/Clinical	Diana Walker, FDA- Statistical review team request subgroup analyses by race, of the effcacy data for studies 405 and 406…
12/18/2008	FDA	Labeling	FDA requesting clarification regarding peel off label on Container and Carton Labeling
12/18/2008	SPI	Labeling	Savient responding to 12/18/08 email regarding peel off label noting that it goes onto patient chart and not iv bag.
12/18/2008	FDA	Labeling	FDA thanking Savient for the quick response to their 12/18/08 info request regarding peel off label on container and carton Labeling. (Email chain begins with email dtd 12/18/08 on line 87.)
12/18/2008	FDA	Info Request/Clinical	FDA Clinical Pharmacology review team requesting the full PK-PD Report for C0403.pdf (See email chain dtd 1/5/09)
12/19/2008	FDA	ACC	FDA requesting status of individuals on the list of consultants and investigators forwarded to them in 12/11/08 email that did not indicate if they are or were former SGE/ACC members.
12/22/2008	SPI	Info Request/Clinical	Response to FDA (Dr. Leibenhaut) queries from 12/18/08 telephone call re: plasma uric acid level assays by CRL and their location, location of the clinical monitoring reports, and data time points for months 3 and 6.
12/22/2008	SPI	PAI	Response to FDA with ground transportation info for PAI in Tel Aviv at BTG for 1/26/09 to 2/5/09
12/22/2008	SPI	PAI	Email sending Itineraries to FDA for PAI Hotel Confirmations for Anderson, Farbman, Chi (Confirmed itineraries attached to email)
12/22/2008	SPI	Info Request/Clinical	**Email submission of 0004** to FDA (Diane Walker) including cover letter and all supporting documents per 12/16/08 request for validationa assays, sops and relevant supporting data.

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12/22/2008	SPI	Amendment/Clinical	**Submission 0004** - Response to 12/16/08 FDA request for assay validation reports for all immunogenicity assays, SOPs for immunogenicity assay and and relevant supporting assay development data.
12/23/2008	SPI	Administrative	Sent FDA w/list of consultants w/wo SGE Status
12/23/2008	SPI	Amendment/Clinical	Sent FDA corrected copy of cover letter for Submission 0004 - Bioanalytical Information Request because pages 12, 13, 14 of the cover ltr, including the summary tables were not included in email submission.
12/29/2008	FDA	General Correspondence	FDA Email forwarding a copy of the FDA's letter accepting the BLA appplication for filing
12/29/2008	SPI	Info Request/Clinical	Email from M. Husain with 9 attachments responding to FDA Statistical RFI and submitted in 0005
12/29/2008	FDA	Acknowledgement	**FDA** letter accepting BLA application and identifying possible review issue regarding cardiovascular deaths and cardiovascular SAEs.
12/30/2008	FDA	Acknowledgement	FDA acknowledging receipt of the email 0005 submission and the electronic 0004 submission.
12/30/2008	SPI	Info Request/Clinical	**Submission 0005** - Response to 12/18/08 FDA Request for subgroup analyses by race for C0405 and C0406. submission provided Summary tables for C0405 and C0406 analyzing subjects by race, treatment regimens and the corresponding responses to the primary end
1/5/2009	FDA	PAI	Discussion regarding postponing PAI at BTG because of ongoing fight between Israel and Hamas; FDA stated that postponment will have no impact on ongoing BLA review, however, PAI is a requirement for BLA approval, and then the action date might be delayed
1/5/2009	FDA	Info Request/Clinical/Tox	FDA acknowledging receipt of Savient's response for info requested in FDA's 12/18/08 email re: the full PK/PD report for C0403 and also noting that FDA didn't think a formal submission was necessary - Clinical Pharmacology
1/6/2009	FDA	Info Request/CMC	FDA confirming it is okay to submit CMC changes as a single amendment as requested in Savient's 1/5/09 email.
1/7/2009	FDA	Info Request/CMC	FDA requesting contact information for Charles River Labs and Kendle and Savient's response on same date with this info.
1/16/2009	SPI	Amendment/CMC	**Submission 0006** - CMC update including analytical procedures because previous versions were submitted in original 0000 in error and providing new source documents for CMC sections 3.2.S.5, 3.2.P.3.3, 3.2.P. 3.4, 3.2.P.5.2, and 3.2. R.1.2
1/22/2009	FDA	Acknowledgement	FDA acknowledging that they received CMC Amendment 0006 and all files transmitted were ok.
1/22/2009	FDA	PAI	Contact Report to discuss January 289 - February 5, 2009 PAI at BTG under Israel's current situation., AAC Meeting scheduled for March and AAC agenda
1/23/2009	SPI	Info Request - Clinical	Email from M. Husain to Diana Walker providing explanation on various tables from ISS and ISE, Treatment Response by disease duration in study C0405/406 CSR Tables 10.11 and 10.12 and explanation of discrepancy in data in ISS and ISE. Provide a subgroup a
1/23/2009	SPI	REMS	Email from M. Husatin to Diana Walker providing outline of REMS tools to be submitted week of 2/2/09: HCP Intro Letter, HCGuide/Brochure,and Patient Guide
1/26/2009	FDA	Proprietary Name	FDA Letter, attached to email dated 1/27/09, accepting KRYSTEXXA
1/27/2009	SPI	REMS	Discussed submitting a revised REMS and Labeling to the BLA

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Date	From	Info Type	Description
1/27/2009	FDA	Proprietary Name	FDA Email from Diana Walker with FDA Acceptance Letter attached for our proposed propietary name, KRYSTEXXA
1/28/2009	SPI	Amendment/CMC	**Submission 0007** - Amendment to a Pending Application: CMC - based on agreement w/FDA at 11/21/06 Type B CMC mtg. to review Km and Kcat specs and additional stablity data prior to BLA approval, and at Pre BLA mtg. on 4/17/08, Div. also agreed Savient could
1/29/2009	SPI	Briefing Book	Discussed submitting reanalyzed data to the BLA and submitting a brief summary in the Briefing Book
1/29/2009	FDA	Amendment/CMC	FDA Email from Diana Walker acknowledging receipt of CMC Amendment 0007
1/29/2009	FDA	Info Request/Clinical	Email FDA Clinical Info Request ref ECGs and requesting that we send to FDA by Tuesday, 2/3/09.
1/29/2009	SPI	Info Request/CMC	Murad Husain will provide FDA with REMS Tools and revised labeling via e-mail by Friday, 1/30/09 followed by eCTD submission on Tuesday of following week
1/30/2009	SPI	Clinical/Labeling/BB	Submission of new PD analysis, CV adjudication and briefing book for AAC...Dr. Simon advised FDA of BLA oversight committee and discussed the organization of BLA and wanted to make more clear certain safety and efficacy information. Dr. Simon informed FDA
1/30/2009	SPI	Clinical/Labeling/BB	**VERSION 2:** Submission of new PD analysis, CV adjudication and briefing book for ACC...Dr. Simon advised FDA of BLA oversight committee and discussed the organization of BLA and wanted to make more clear certain safety and efficacy information. Dr. Simon i
2/1/2009	SPI	Briefing Book	Briefing Book dated February 1, 2009 for FDA AAC Meeting being held on March 5, 2009 at the Hilton in Silver Spring, MD. 35 CDs and 12 paper copies (hand delivered).
2/2/2009	SPI	Briefing Book	Receipt of SPI letter to Nicole Vesely with delivery of 12 paper copies of Briefing Book and 35 CD's with Briefing Book.
2/3/2009	FDA	Briefing Book	Email from Nicole Vesely suggesting 2 options for removing appendices from Briefing Book
2/4/2009	CRL	PAI	Letter from Charles River Labs to FDA confirming PAI for March 23 to 27, 2009
2/4/2009	SPI	Amendment/Clinical	**Submission 0008 –Response to FDA Requests for Information from January 23, 2009, Addendum to Risk Management Plan, Cardiac Adjudication and Revised Labeling** - request for an addendum to Risk Mgt. Plan and corresponding tools. Jan. 22, 2009 Tcon discussed
2/5/2009	SPI	Info Request/Clinical	TCON with FDA (Murad Hussain, SPI and Diana Walker, FDA) Purpose to discuss Revised REMS and Labeling.
2/6/2009	SPI	Amendment/Clinical	**Submission 0009** - Response to FDA Request for Information – Clinical- FDA 1/29/09 communications requesting we provide explanation how screening and Wk 25 ECGs were interpreted, requested a narrative explanation how categories were defined in Table A21
2/9/2009	FDA	PAI	Email from Oumou K. Barry, Associate Director, Field Investigations, FDA, informing us CRL confirmed 3/23/09 to 3/27/09 for inspection.
2/11/2009	FDA	120-Day Update	Email from FDA responding to request to delay 120-Day Safety Update by a week.
2/17/2009	FDA	Administrative	FDA Letter regarding extending PDUFA date to August 1, 2009
2/18/2009	FDA	Clinical	Email from FDA requesting submission of datasets and validation be submitted as a SAS transport file and received by FDA by Tuesday, 2/24/09
2/19/2009	FDA	Amendment/CMC	Email from FDA in response to Mfg qualification. FDA suggested we submit protocol to qualify alternative Mfg site for Pegloticase as a CMC Amendment to IND
2/24/2009	SPI	Info Request/CMC	Email from G. Savvas from CMC forwarding 3 attachments: Notification to CDER and OPD for Change of Sponsor Name and Importer for pegloticase DS (API).

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Date	From	Info Type	Description
2/25/2009	SPI	Administrative	Email from Mary Farbman regarding FDA Guide to International Inspection and travel
2/25/2009	FDA	Info Request/CMC	Email from Diana Walker, FDA, regarding upcoming comments from reviewers of CMC section of BLA
2/26/2009	FDA	Clinical	Email from Diana Walker agreeing to proposed timeline for Clinical (EKG and Cardiac Adjudication) submission on March 12, 2009
2/27/2009	SPI	Safety Update	**Submission 0010** - 120-day update to FDA in 0010
2/27/2009	SPI	Amendment/Clinical	**Submission 0011** - Response to Request for Information PK Data and datasets
2/27/2009	SPI	120-Day Update	**Submission 0012** - Error in Lifecycle Operator in 120-Day Safety Update
3/3/2009	SPI	Acknowledgement	Email from M. Husain confirming that Sequence 0012 is the correct 120-day safety update.
3/3/2009	FDA	PAI	FDA obtaining clearances for a June 3 - June 11 PAI at BTG. Will confirm at a later date
3/4/2009	FDA	PAI	Email from FDA thanking us for recommending the US Embassy Israeli Website for travel.
3/5/2009	FDA	Info Request/Clinical/Tox	BLA 125293 Nonclinical information request -- requesting amendment to Covance Report 7533-100 and final report regarding vacuoles
3/5/2009	FDA	Info Request/CMC	FDA requesting info regarding product quality and manufacturing Information Request - Microbiology CMC defiencies in BLA re: Fermentation steps, purification steps, PEGylation steps, formulation/filration...etc.
3/5/2009	FDA	Info Request/CMC	Email clarifying that info request in earlier 3/5/09 email should be submitted to Module 3.
3/10/2009	FDA	Acknowledgement	FDA Email stating that once 0013 is received she will forward to the Clinical Team
3/10/2009	SPI	Amendment/Clinical	Email to FDA with Cover Letter of 0013 regarding FDA questions on EKG - official submission sent on 3/10/09.
3/10/2009	SPI	Amendment/Clinical	**Submission 0013** - Response to Request for Information - Clinical CV Questions
3/13/2009	FDA	Info Request/CMC	Email from FDA requesting LOA from Sartorius DMF 5967, info and summary data for sterilization validation of 20L LDPE receiving bag, and info on integrity of bag's post-sterilization
3/17/2009	SPI	Info Request/CMC	Savient asking for clarification to Question 4b in Email dtd 3/5/09
3/18/2009	SPI	Info Request/Clin	Email stating 0014 cover letter and catheterization report is attached
3/18/2009	FDA	Info Request/CMC	FDA stating that Product Quality reviewer confirmed that Savient's response was sufficent in 3/17/09 email regarding question 4b re PEGylation steps.
3/18/2009	SPI	Info Request/CMC	Requesting FDA to grant a week delay in responding to 3/5/09 questions.
3/19/2009	FDA	Info Request/CMC	FDA confirming Savient can submit FDA info request - microbiology on April 3. Also FDA requested clarification on PI, Savient changed section 17.3 to Medication Guide...ok w/FDA but wanted to clarify our intent.
3/19/2009	SPI	Amendment/Clinical	**Submission 0014** - Response to RFI - Clinical
3/20/2009	SPI	Info Request/CMC	Responding to 3/19/09 email thanking for extension for CMC Amendment filing and Savient response re error in PI.
3/20/2009	FDA	Info Request/CMC	FDA responding to 3/20/09 email reference CMC comments from reviewers and PI error. Ms. Walker going to talk with Dr. Siegel and suggesting we wait and make corrections/rev. during labeling discussions to cut down on number of submisisons and confusion.
3/23/2009	SPI	Info Request/CMC	Savient requesting names of primary microbiology reviewer and supervisory reviewers for BLA.
3/24/2009	FDA	Info Request/CMC	FDA responding that if Savient needs to communicate with reviewers, to let Ms. Walker know and she will arrange a TCON.

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3/25/2009	SPI	Info Request/CMC	Savient responding to Division recommendations to add 0.2 um filters and requesting a brief Tcon with Review Microbiogist and CMC reviewers.
3/27/2009	FDA	Info Request/CMC	FDA responding to 3/24/09 email and responding to the 2 questions in that email (0.2up filtration, and commercialization of six lots...)
3/30/2009	SPI	PAI	Savient sent updated BTG Mfg. schedule for PAI in June.
3/31/2009	FDA	PAI	FDA confirmed receipt of updated Mfg schedule, stated no further requests and send schedule as amendment to BLA.
4/3/2009	SPI	Administrative	Email from Mary Farbman requesting Savient to make hotel reservations for PAI at BTG...M. Husain responding on same date confirming that Savient will be happy to do so.
4/3/2009	SPI	Amendment/CMC	Email to FDA confirming Savient will arrange hotel reservations and ground transportation.
4/3/2009	SPI	PAI	Email to FDA forwarding copy of Sequence 0016 cover letter which provides the Mfg. schedule for upcoming PAI in June 2009. See Sequence 0016 for cover letter attached to email.
4/3/2009	SPI	Amendment/CMC	**Sequence 0015** - Response to FDA Request for Information-CMC/Microbiology
4/3/2009	SPI	Amendment/CMC	**Sequence 0016** - Manufacturing Schedule for Pegloticase Drug Substance for Pre-Approval Inspection (2009) at BTG
4/6/2009	FDA	Acknowledgement	FDA acknowledging receipt of Sequence 0015 and 0016 and that they were forwarded to the appropriate review team members.
4/8/2009	SPI	Amendment/Clinical	**Sequence 0017** - Submitted to FDA Audited final immunohistochemistry report - PAI Study No. IM1678 as an amendment to Covance 7533-100 and a Summary Report prepared by Hugh Black
4/17/2009	FDA	Info Request/CMC	Product Quality & Mfg Info Request - Microbiology CMC deficiences - Drug Product: Issue 1. confirm psi pressure inside vessel (PPD); Issues 2-3 provide summary data: for validtion info on more challenging microbial ingress study re media fill run #8171, t
4/17/2009	SPI	PAI	Savient sending to FDA reassessed mfg schedule for June PAI.
4/17/2009	FDA	PAI	Savient sending to FDA reassessed mfg schedule for June PAI.
4/20/2009	SPI	Administrative	Email from M. Husain to P. Hamelin regarding conversation with FDA, Diana Walker, regarding upcoming submissions and her response (mfg. schedule, REMS. EKGs) .
4/20/2009	SPI	Administrative	M. Husain informing FDA re: upcoming submissions (mfg schedule, report on EKGs, revised REMS, and request for TCON re BB and presentation at AAC.
4/21/2009	SPI	Administrative	Email to FDA forwarding copy of Sequence 0020 cover letter. (See Sequence 0020)
4/21/2009	SPI	Amendment/CMC	**Sequence 0018** - Revised mfg. schedule for June BTG PAI
4/21/2009	SPI	Amendment/Clinical	**Sequence 0019** - Per 3/10/09 communication responding to Agency request to review abnormal exit EKG...submitting QT study from independent cardiologist of all EKGs for C0405 & C0406.
4/22/2009	SPI	Administrative	**Sequence 0020** - Points for Discussion prior to the AAC Mtg.: focus of communication is the disseminationof key elements of AAC BB and AAC presentation. Submission included questions to help in preparation for upcoming TCON.
4/27/2009	FDA	Administrative	FDA confirming TCON for 4/29/09 at 1 pm (EST).
4/28/2009	SPI	Info Request/CMC	Sending an advance copy of Sequence 21 letter requesting TCON to discuss KM/kcat assay.
4/28/2009	SPI	ACC	Savient sending revised list of consultants attending AAC mtg.
4/29/2009	FDA	ACC	FDA initiated: FDA's response to Savient questions submitted on 4/21/09 about the briefing book and upcoming AAC meeting.
4/29/2009	FDA	Acknowledgement	FDA acknowledging receipt of 4/28/09 email and stating they will forward Sequence 21 letter to CMC team re TCON.
4/29/2009	SPI	Amendment/CMC	**Sequence 0021**- Request for CMC Teleconference w/FDA CMC review team to discuss the KM/kcat assay...

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5/5/2009	FDA	Administrative	Email from FDA responding to 0021 request for TCON...CMC reviewers do not feel it is neessary at this time. See 4/28/09 email to FDA sending copy of Sequence 0021.
5/5/2009	SPI	Info Request/CMC	FDA requested location of info in BLA in 5/5/09 email and Murad responded with location on same date...see email chain.
5/6/2009	FDA	ACC	Email from FDA reminding Savient that AAC background package due to FDA on 5/14/09 and Savient's acknowledging receipt of response and othe emails re AAC meeting.
5/6/2009	FDA	ACC	Email from N. Vesley w/attached list of Savient consultants attending AAC in June.
5/7/2009	FDA	ACC	FDA (N. Vesely) responding to M. Husain 5/6/09 email asking when FR announcement will be published and noting it will officially publish 5/8/09...also providing mtg room set up, materials needed and FDA requesting names and affiliations of speakers by Jun
5/7/2009	FDA	ACC	Email from FDA informing Savient that they don't provide INR with background package for AAC meeting and informing Savient that Dr. D. Bruce Burlington will be the IR at meeting.
5/8/2009	SPI	Info Request/CMC	Savient asking FDA for clarification of Question #2 in 4/17/00 email regarding CMC info requestt
5/11/2009	SPI	Info Request/CMC	Savient asking again if CMC reviewer could provide clarification to Q2 in 4/17/09 FDA email info req.
5/12/2009	SPI	Info Request/CMC	**Sequence 0022** - Response to FDA Request for Information CMC/Microbiology.
5/14/2009	SPI	Briefing Book	Briefing Document for Arthritis Advisory Committee Meeting, June 16, 2009
5/18/2009	FDA	Info Request/CMC	FDA CMC responding to Savient request for clarification re Q2 in 5/8/09 email.
5/18/2009	FDA	Info Request/CMC	Chain of emails 5/18/09 through 4/17/09 (G. Zhu) with FDA subject: "Refusal of Admission" on Entry #231-96095445"...FDA informing Savient Compliance officer contacted and it is still under review.
5/19/2009	FDA	PAI	FDA Letter emailed with EIR for East Brunswick NJ covering conduct of clinical study C0405 and C0406
5/28/2009	FDA	Info Request/CMC	Email from FDA re Chemistry/Product information request and requesting info by no later than June 11, 2009.
5/29/2009	SPI	Info Request/CMC	Email responding to FDA's 5-28-09 Chemistry Info Request email and seeking clarification of the FDA's request.
5/29/2009	SPI	PAI	Email from Savient responding to FDA's 5/27/09 email regarding travel info and logistics for upcoming PAI BTG inspection first week of June 2009. (See chain of emails)
6/1/2009	FDA	Info Request/CMC	Email from FDA responding to Savient 5/28/09 chemistry clarification.
6/3/2009	FDA	Info Request/CMC	Email from FDA requesting Microbiology CMC deficiencies for Savient BLA, STN 125293/0: Drug Product to be submitted to the FDA no later than Wednesday, June 17, 2009
6/4/2009	SPI	Briefing Book	Letter to FDA w/attachments - Errata to FDA Briefing Book and Errata to Savient briefing book for Arthritis Advisory Committee meeting scheduled for June 16, 2009.
6/11/2009	SPI	Info Request/CMC	Email to D. Walker at email attaching the cover letter for Sequence 0023 and informing the FDA it will be formally submitted today by the gateway.
6/11/2009	FDA	Info Request/CMC	FDA email acknowledging timely submission to their June 1, 2009 Chemistry clarification request responses.
6/11/2009	SPI	Amendment/CMC	**Sequence 0023** - Reponse to FDA request for information- CMC reference the FDA's May 28, 2009 Email requesting clarification of information provided in BLA and subsequent amendments.
6/12/2009	FDA	General Correspondence	Email from FDA regarding FDA presentation slides before teleconference

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6/15/2009	FDA	General Correspondence	Email from FDA confirming they will correct BLA # error and re-post correct # on website. FDA responding to Savient's June 14, 2009 email informing them of error which is part of this email chain.
6/15/2009	FDA	Briefing Book	Email from FDA with Addendum to their briefing package
6/17/2009	SPI	Info Request/CMC	Email to FDA responding to June 3, 2009 email requesting Microbiology Information Request. This email responds to FDA comments 1, 3, 4, 5, and 6 in the June 3, 2009 email. Response to comment #2 will be submitted with formal amendment.
6/17/2009	SPI	PAI	Email to FDA confirming FDA's requested items, sending list of items discussed and Savient requesting FDA's confirmation that the proposals to fulfill these requested items are accurate and acceptable.
6/18/2009	FDA	PAI	Email from FDA, Diana Walker, confirming she has forwarded our email dated 6/17/09 "Requested Items form Dr. Farbman" to Dr. Farbman. Dr. Farbman will contact us with her comments to our responses.
6/18/2009	FDA	PAI	Email from FDA Diana Walker, items 1 through 8 being reviewed, Dr. Farbman confirmed that items 9, 10, and 11 are required and request we submit them by email followed by official submission.
6/18/2009	SPI	Info Request/CMC	Email with response to Microbiology Request sent in Sequence 0024
6/18/2009	SPI	Info Request/CMC	Email attaching Items 9, 10, and 11 requested by M. Farbman of FDA.
6/18/2009	SPI	Amendment/CMC	**Sequence 0024** - Response to FDA Request for Information - CMC (see June 3, 2009 email from D. Walker at FDA requesting clarifications of microbiological info provided in BLA)
6/19/2009	SPI	Info Request/Clinical	Email to FDA ref June 17 2009 Immunology Information request...formal submission Sequence # 0025 will be submitted on June 22, 2009 (this file includes attachment)
6/22/2009	SPI	Amendment/Clinical	**Sequence 0025** - Amendment - Clinical in response to June 17, 2009 FDA request. Savient provided Interim Progress Report of Anti-uricase Antibody Assays in Two Phase 3 Clinical Studies (C0405 & C0406).
6/23/2009	FDA	Info Request/CMC	Email from FDA confirming when to submit specific documents described in Sequence 0024 in table on Page 6.
6/23/2009	SPI	Amendment/CMC	**Sequence 0026** - Response to FDA Request for Information - CMC - Responding to FDA June 18 and 19, 2009 emails. Submitting list of submission timelines and documents requested by Dr. M. Farbman from FDA at PAI during BTG in June 2009.
6/24/2009	FDA	Info Request/CMC	TCON initiated by FDA: Purpose: Peglylation Process difference between Phase 3 Clinical and Comercial Batches - ref FDA's email dtd. June 19, 2009.
6/25/2009	FDA	General Correspondence	Email chain on 6/25/09 regarding FDA having problems with ESG receiving submissions. This chain of emails is regarding Sequence 0027. Diana Walker informing M. Husain that she was notified the FDA had received sequence 0027 at 2:43 pm on 6/25/09.
6/25/2009	SPI	Amendment/CMC	**Sequence 0027** - Responding to FDA June 23, 2009 email requesting submission of remaining four documents under items 1, 2, 3, and 5 previously tabulated in Sequence 0024. See Sequence 0026, 0024 and 0015 for all documents requested by FDA. Document associ
6/26/2009	FDA	Info Request/CMC	CMC Information request - Reference batch 568200310...reviewers requesting Savient to address comparability issues between products...
6/26/2009	SPI	Amendment/Clinical	**Sequence 0028** - Response to FDA Request for Information - Clinical - ref stopping rule..
6/29/2009	FDA	Info Request/CMC	Email from FDA ref Savient request for TCON to discuss FDA 6/26/09 email regarding CMC issues.
6/30/2009	FDA	Info Request/CMC	Email from FDA Microbiology Information Request...requesting deficiencies to be addressed with an amendment to the BLA
7/1/2009	FDA	Info Request/Post Marketing	FDA Request for Information/potential PMR proposals

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Date	From	Info Type	Description
7/1/2009	FDA	Labeling	Email from FDA regarding draft label.
7/7/2009	SPI	Info Request/Post Marketing	Email requesting clarity regarding July 1, 2009 email regarding post-marketing proposals.
7/8/2009	FDA	Info Request/Post Marketing	Email from FDA responding to 7/7/09 Savient email asking for clarity regarding PMR proposals...Dr. Siegel responded to questions 1 and 4 and Dr. Mellon will discuss # 2 during TCON.
7/8/2009	SPI	Amendment/CMC	**Sequence 0029** Response to FDA Request for Information - CMC and Stability Update - commitment made to Agency at Type B CMC Mtg on 11/21/2006, submitting real time stability data for the drug product for up to 24 mons...
7/9/2009	FDA	Info Request/CMC	Email from FDA requesting timeline for Savient's response to the agency's June 30, 2009 microbiology information request. This is a chain of emails dtd 7/9/09 responding to that request and why the delay and informing FDA that Savient will respond on 7/1
7/10/2009	FDA	Info Request/Post Marketing	FDA initiated: Post-marketing required (PMR): Toxicology Study
7/10/2009	SPI	Labeling	Email to FDA forwarding Clean copy of draft labeling per July 1, 2009 FDA request and forwarding draft PI Labeling per July 1, 2009 FDA request. (See July 1, 2009 email from FDA)
7/10/2009	SPI	Info Request/CMC	Email to FDA in response to FDA's June 26, 2009 request for CMC information...also included dial in numbers for July 13, 2009 TCON with FDA.
7/10/2009	SPI	Amendment/CMC	Email from Savient forwarding a copy of Sequence 0030 coverletter.
7/10/2009	SPI	Amendment/CMC	**Sequence 0030** - Response to FDA Request for Microbiology Information...responding to June 30, 2009 email from FDA requesting additional microbiological in-process controls in the drug substance mfg. process.
7/13/2009	SPI	Info Request/Post Marketing	Email responding to FDA July 1, 2009 email request for information/potential PMR Proposals - two requests for post-marketing proposals from the Division, Clinical and Non-Clinical. (Email chain includes July 1, 2009 email from FDA)
7/15/2009	FDA	General Correspondence	Email from FDA responding to 7/15/09 email from M. Husain requesting status of CMC info req, labeling group, and PI. FDA provided an update regarding these issues. (See July 15. 2009 email chain with FDA)
7/15/2009	FDA	General Correspondence	Email chain between FDA and Savient regarding status of items...FDA indicating that the CMC info requests submitted by email may not need to be submitted as formal amendments to BLA. Responding to M. Husain's inquiry of July 15, 2009...(See email chain)
7/15/2009	FDA	General Correspondence	Email from FDA...CMC/Product requested that we submit CMC responses as amendment for the record. (See Sequence 0031)
7/17/2009	SPI	Amendment/CMC	Email to FDA forwarding formal Sequence 0031 Amendment cover letter to FDA as requested in the July 15, 2009 email.
7/17/2009	SPI	Amendment/CMC/ Clinical	**Sequence 0031**- Response to FDA Request for CMC Information: Responding to June 26, 2009 email from FDA requesting Savient to address 4 CMC Comments regarding batches of KRYSTEXXA.
7/27/2009	FDA	General Correspondence	Responding to telephone message regarding status of several items, including Action letter.
7/29/2009	FDA	Acknowledgement	FDA initiated: Heads-up for PDUFA action.
7/31/2009	FDA	General Correspondence	Email from FDA Forwarding Action letter for BLA 125293. Original ltr sent via US mail.
7/31/2009	FDA	General Correspondence	FDA's Complete Response Letter regarding approval of Krystexxa.
8/6/2009	FDA	General Correspondence	Email from FDA clarifying what we need to include in our meeting request.

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8/6/2009	FDA	General Correspondence	FDA respond acknowledging 8/6/0-9 email from Savient forwarding copy of our Type A Meeting Request letter...official submission will follow.
8/6/2009	SPI	General Correspondence	Savient responding to 8/6/09 FDA email tentatively scheduling 9/14/09 Type A Meeting Requst.
8/6/2009	SPI	Administrative	**Sequence 0032** Request for a Type A Meeting- requesting meeting to address issues in CRL
8/7/2009	SPI	General Correspondence	Savient confirming that they prefer September 14 for Type A meeting
8/10/2009	FDA	Efficacy Supplement	FDA inquiring if we are submitting mtg request week of 8/10/09
8/10/2009	SPI	General Correspondence	Savient informing FDA official meeting request sent by ESG
8/10/2009	FDA	General Correspondence	FDA acknowledging receipt of mtg request through Gateway
8/10/2009	FDA	General Correspondence	Letter from FDA granting Type A Meeting, scheduled for 9/14/09
8/11/2009	FDA	General Correspondence	FDA email frowarding copy of Meeting Granted letter dtd. August 10, 2009...original will be received by mail. (See 8/10/09 entry below)
8/24/2009	FDA	Info Request/CMC	Email from FDA: TCON 8-27 discussin topics: OLE lots, reference the 12 lots of drug substance with high levels of bioburden, and requesting we describe intentions Ph 3 mfg process or conduct bridging studies linking the Ph 3 materials, etc.
8/25/2009	SPI	General Correspondence	**Sequence 0033** Type A Meeting: September 14, 2009 Briefing Document - outlining specific objectives and outcomes for discussion at 9/14/09 mtg. and includes the hard copies and CDs of the briefing materials for meeting.
8/26/2009	SPI	Info Request/CMC	Email to FDA responding to their 8/24/09 email regarding 8/27/09 TCON Disc. Topics and responding to requests regarding Drug Product Lots, BLA resubmission plans , dial in #'s for TCON and who from Savient will participate in TCON on 8/27/09.
8/27/2009	FDA	Info Request/CMC	FDA initiated: Restriction on Manufactured DP Batches
8/27/2009	FDA	Info Request/CMC	Email from FDA after 8/27/09 TCON requesting Savient to state verbal commitment to destroy/discard any batches/lots of drug that havehigh bioburen levels and to submit as an amendment to BLA.
9/2/2009	SPI	Info Request/CMC	Email to FDA provide clarity and relevant information regarding the FDA's request in e-mail dated 27 August 2009 for Savient to destroy certain pegloticase Drug Product batches (12 batches of Process B Drug Substance)...etc.
9/11/2009	FDA	Administrative	Email from FDA forwarding official ltr attaching division's responses to Savient's questions from meeting package for 9/14/09 Typa A Meeting.
9/11/2009	SPI	Administrative	Email to FDA thanking for responses to sponsor's questions for type A meeting on 9/14/09 and confirming that sponsor does not want to change anything regarding that mtg.
9/11/2009	FDA	Administrative	Email from FDA reference Mass Spectra...attaching Appendix I Mass Spectra...FDA acknowleding we submitted this information on July 10, 2009 according to their info request dtd June 26, 2009.
9/11/2009	FDA	Administrative	FDA letter with Division's responses to Savient's questions from meeting package for 9/14/09 Type A Meeting.
9/13/2009	SPI	Administrative	Attaching word copy of list of topices that sponsor would like to review at 9/14/09 Type A Meeting. (Attachment included with link)
9/18/2009	FDA	Administrative	Email from FDA: Advice on REMS Submission 18Sep09 - comments for Sponsor from office of Surveillance & Epidemiology, DRISK, ref REMS proposal in Savient's briefing package provided for 9/14/09 Type A Mtg. Comments were in ref to REMS Goals, Medication Gu
9/22/2009	SPI	Administrative	**Sequence 0034** Type A Meeting Minutes with Sponsor's comments

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9/25/2009	SPI	Amendment/CMC	**Sequence 0035** Disposition of Drug Product Batches - sponsor committing to destroying batches with high bioburden and summarizing what it will do with the remaining in quarantine at Enzon or Fisher Clinical Svcs.
10/6/2009	FDA	Administrative	FDA sending official copy of September 14, 2009 Type A Mtg. minutes.
11/18/2009	SPI	General Correspondence	Email sending copy of Sequence 0036 regarding Type A Meeting Minutes: Proposal for Revision.
11/18/2009	SPI	General Correspondence	**Sequence 0036 Type "A" Meeting Minutes: Proposal for Revision:** Requesting a modification of minutes from 9/14/09 meeting minutes.
12/14/2009	FDA	General Correspondence	FDA reviewers' agreed to Savient's Meeting Minutes revisions for Type A Meeting. Formal letter will be issued in Jan 2010.
1/11/2010	FDA	General Correspondence	Email from FDA forwarding letter regarding their response to Sequence 0036 Type A Meeting Minutes: Proposal for Revision.
1/11/2010	FDA	General Correspondence	Letter from FDA regarding request for modification of minutes for 9/14/09 meeting, and agree to the proposed mofication of minutes in Question 2c of those minutes...
2/5/2010	FDA	General Correspondence	Email from FDA confirming formatting of revisions for resubmission.
3/9/2010	SPI	General Correspondence	TCON to inform FDA about BLA resubmission Week of March 15, delay of pegloticase IND AR. During TCON FDA informed Svt of FDA restructure.
3/11/2010	FDA	Administrative	Intro to new project manager at FDA, Badrul Chowdhury
3/12/2010	FDA	Administrative	FDA confiming name and address of new Director, Badrul Chowdhury.
3/15/2010	SPI	General Correspondence	Email to FDA informing we sent Seq. 0037 BLA resubmission through FDA Gateway through eCTD vendor ISI.
3/15/2010	SPI	Info Request/Clinical/CMC	**Sequence 0037 Response to the July 31, 2009 Complete Response Letter -** provide additional CMC info and a Safety Update, including Labeling, REMS, and Medication Guide according to mutual agreements reached at Type A mtg between FDA and SPI in Sept 2009.
3/17/2010	FDA	Acknowledgement	FDA confirming receipt of Sequence 0037 BLA resubmission
3/29/2010	FDA	Acknowledgement	FDA emailing a copy of "Acknowledge Complete Response" letter indicating they received and accepted BLA resubmission and consider this a complete, class 2 response to the FDA action letter...and that 9/14/10 is the user fee goal date.
3/29/2010	FDA	Acknowledgement	FDA "Acknowledge Complete Response" letter indicating acceptance and designating the BLA resubmission as a Class 2 review with PDFA date of 9/14/10.
4/12/2010	SPI	Administrative	Email contact report from S Hamburger regarding voicemail request from FDA T. Phlhaus asking for the name of the Head of the Eurosequence facility.
4/14/2010	SPI	Administrative	Email contact report from S. Hamburger informing staff that he provided T. Pohlhuas of FDA with the Henk J. Bak, PhD, contact information.
4/15/2010	FDA	General Correspondence	Email from FDA reference Savient's request to clarify 2 questions related to the April 14, 2010 request from FDA when preparing the reply (see Submission, Sequence 0038) (Email chain beginning 4/7 and ending with 4/15/10 emails regarding IR 1 & 2)
4/23/2010	SPI	General Correspondence	**Sequence 0038 General Correspondence: Response to Apr 14, 2010 E-Mail Requests** to provide a brief summary to each issue identified in CRL and provide changes made to the CMC portion that were not part of the response to CRL.
5/21/2010	SPI	General Correspondence	Email forwarding S. Hamburger's email to FDA with letter from BTG dtd. 5/20/10 letter informing FDA corrective actions for the observations in Form FDA 483 from PAI June 2009 have been completed except for ongoing studies.

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5/25/2010	SPI	General Correspondence	Email from S. Hamburger forwared by M. Husain to FDA R. Sista, to provide clarification of CMC items tofacilitate the FDA review of KRYSTEXXA.
5/25/2010	FDA	Info Request/CMC	Email from FDA: BLA 123293-Peglotiase IR-3 - Requesting CMC microbiology information by noon of June 1, 2010.
6/1/2010	FDA	General Correspondence	FDA responding to 5-25-10 email requesting clarification regarding 3 Month CMC update and other issues with CMC
6/1/2010	SPI	General Correspondence	**Sequence 0039: General Correspondence: Response to May 25, 2010 E-Mail Requests** regarding validation of equipment
6/4/2010	FDA	Info Request/CMC	Information Request 3 - FDA requesting by COB 6/25/10 a study of the PennTech vial washer be done to provide uantitative data demosnstrating rmeovel of spiked sodium chloride on KRYSTEXXA vials from 3 wash cycles.
6/7/2010	SPI	General Correspondence	**Sequence 0040 General Correspondence: CMC Update** amendment replacing Regional Information Section CTD 3-2-R -updating Table 3 of leaf because BTG updated manufacturing SOPs and in Sequence 0037, Table 3 Savient inadvertently did not include a few SOP r
6/16/2010	SPI	General Correspondence	**Sequence 0041 General Correspondence: Response to FDA Request on Vial Washer -** responding to Division's June 4, 2010 email request regarding PennTech vial washer at Sigma-Tau PharmaSource…
7/1/2010	SPI	General Correspondence	Subject: KRYSTREXXA BLA review cycle questions…asking for TCON to confirm the new divisions timeline regarding our responses to the FDA's information requests.
7/2/2010	SPI	General Correspondence	**Sequence 0042 General Correspondence: Response to FDA Request on Vial Washer** - Questions to FDA regarding SigmaTau PharmaSource's to provide report with info regarding sodium chloride; requesting agreement to submit report in ealry August 2010 regarding
7/12/2010	SPI	General Correspondence	Pegloticase: Specific Activity, KM and kcat by Product Accumulation and KM and kcat by Substrate Depletion assays (Acceptance criteria) - Information
7/13/2010	SPI	Administrative	Email from S. Hamburger to P. Hamelin, M. Husain, P. Yachmetz, P. Clarke regarding phone mail message to FDA, Dr. Sista asking for feedback to Savient's Jul 1, 2010 email request related to the status of the review from all disciplines and regarding email
7/13/2010	FDA	General Correspondence	Edmail responding to July 1, 2010 email from S. Hamburger regarding KRYSTEXXA BLA review cycle questions.
7/20/2010	SPI	General Correspondence	Email to R. Sista at FDA regarding Savient's Key questions for BLA review, e.g., PAI of BTG facility scheduling, 483 for Eurosequencing and other CMC questions.
7/21/2010	SPI	Administrative	Email to P. Hamelin, P. Yachmetz, P. Clarke regarding voicemail message to Dr. Sista at FDA: Phone call notes to Dr. Ramani Sista (FDA): 21 July 2010 Regarding 20 July 2010 email questions.
7/27/2010	SPI	Administrative	Email to FDA regarding phone message made by S. Hamburger to Dr. Sista of FDA informing her that the Updated Stability Data would be submitted on Wednesday, July 28, 1010.
7/28/2010	SPI	General Correspondence	**Sequence 0043 General Correspondence: Updated Stability Data** (3- 6 months stability updated data)
7/29/2010	SPI	Administrative	**FDA Contact: July 29, 2010** - To P. Hamelin, P. Clarke, P. Yachmetz, M. Husain - S. Hamburger called FDA and left vm and at 1:45 PM FDA/Dr. Sista returned call. She inquired if we had started the 18-month dog study and was informed Savient had not although
7/30/2010	FDA	General Correspondence	**FDA Email** responding the Key Questions from Savient Regarding KRYSTEXXA (pegoloticase) BLA review...FDA responses follow al ter each questions in Savient's 7/20/10 email
7/30/2010	SPI	General Correspondence	**Savient email** acknowledging receipt of the 7/30/10 email from FDA regardidng key questions.
7/30/2010	FDA	General Correspondence	**FDA email** responding to Q7 as promised in earlier 7/30/email from Dr. Sista, FDA (Key Questions from Savient to FDA)

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8/4/2010	SPI	General Correspondence	**Sequence 0044: General correspondence: Response to FDA Request for Additional Data for PennTech Vial Washer**submitted final reports for the PennTech Vial Washser fro SigmaTau Pharmaceuticals.
8/4/2010	SPI	Administrative	S. Hamburger to P. Hamelin, P Yachmetz, M Husain, and P Clarke....called FDA and left VM regarding Sequence 0044 was sent on this date and which FDA requested be submitted by 8/6/10 and to inform h=them regarding the status of the assay from Eurosequence
8/13/2010	SPI	Administrative	**Phone Contact: August 13, 2010 10 am.**: S.Hamburer left vm with Dr. Sista requesting time to discuss logistics regarding the next 30 days before the 9/14/10 PDUFA date.
8/18/2010	SPI	Administrative	**Email** from QA at Savient regarding FDA inspection at Core Labs...confirming inspection finished and no 483's received.
8/30/2010	FDA	General Correspondence	FDA DMEPA completed their review of cart and container lables and PI and identified deficiencies... see Sequence 0047 for response.
9/2/2010	SPI	General Correspondence	**Sequence 0045 - GENERAL CORRESPONDENCE: Withdrawal of Qualification Protocols for Pegloticase and Uricase Reference Standard** (PRT-QA-074, BLA Section 3.2.s.5 and PRT-QA-075, BLA Section 3.2.s.5)
9/2/2010	SPI	General Correspondence	**Sequence 0046 - GENERAL CORRESPONDENCE: Letter of Intent to Perform CMC Post Marketing Commitments and Phamracology/Toxicology Post Marketing Requirements**
9/3/2010	SPI	General Correspondence	Sequence 0047- GENERAL CORRESPONDENCE: Response to Discipline Rview: Carton Lables (outer and Inner), Peel-off Label and Container Label
9/8/2010	SPI	General Correspondence	**Sequence 0048 - General Correspondence: Updated Letter of Intent to Perform CMC Post Marketing Commitments and Pharmacology/Toxicology Post Marketing Requirements**(See Sequence 0046 too)
9/8/2010	SPI	General Correspondence	**Sequence 0049 - General Correspondence: Letter of Intent to Perform Clinical Post Marketing Requirements**
9/10/2010	SPI	General Correspondence	**Sequence 0050 - General Correspondence:Final Draft KRYSTEXXA Carton labels (outer and inner), Peel-off Label and Container Label; Final Draft KRYSTEXXA Medication**
9/14/2010	SPI	General Correspondence	**Sequence 0051 - General Correspondence: Final KRYSTEXXA Full Prescribing Information**
9/14/2010	SPI	General Correspondence	**Sequence 0052 - General Correspondence: Letter of Intent for CMC, Clinical and Non-clinical Pharmacology/Toxicology Post Marketing Requirements/Commitments**
9/14/2010	SPI	General Correspondence	**Sequence 0053 - General Correspondence: Final REMS and Attachments AND REMS Supporting Document**
9/14/2010	FDA	General Correspondence	**BLA Approval**